COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON MONOPOLY

OF THE

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

NINETIETH CONGRESS

SECOND SESSION

ON

PRESENT STATUS OF COMPETITION IN THE PHARMACEUTICAL INDUSTRY

PART 7

APRIL 23, 24, AND MAY 1, 1968

FIRST OF TWO VOLUMES ON INDOMETHACIN—
TRADE NAME: INDOCIN

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Morning session 2875

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

TUESDAY, APRIL 23, 1968

U.S. Senate,
Monopoly Subcommittee of the
Select Committee on Small Business,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:15 a.m., in room 2221, New Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senators Nelson, Scott, and Hatfield.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator Nelson. We will open the hearings of the Monopoly Subcommittee. The hearings before our Monopoly Subcommittee have shown that there are two serious problems which must be solved to protect the health of the public.

The first problem is the dependence of the FDA and the medical profession on the pharmaceutical industry for information about drugs. The FDA does not engage in drug testing; it approves new drugs solely on the basis of information supplied by the drug industry. It is totally dependent—at present—on the industry which it was established to regulate. In many respects, the medical profession also relies on the drug firms for its information on drugs. There is literally no place from which physicians can get complete, unbiased, objective information about a drug: how it works; what it is good for; how it compares with other drugs in the treatment of a particular illness; and its side effects. The Medical Letter, an independent publication, which sponsors very fine scientific, controlled studies on drugs and which is published twice monthly, is read by only a small fraction of the medical profession and covers relatively few drugs.

One of the main interests of the drug industry, of course, is to put new drugs on the market and to make a profit on their sales. Thus, it cannot be assumed that the information given to the FDA and the medical profession is free from commercial bias. Any careful examination of drug promotional literature will, in fact, disclose that it is not objective—and it would be unrealistic to expect strict objectivity.

The danger inherent in this situation is very great indeed. We have already seen in our hearings on chloramphenicol how advertising and promotion have resulted in widespread use of a dangerous drug for nonindicated cases; how its side effects have been played down; and how many innocent people have suffered. Both the medical profession and the public have been misled with respect to the use of this drug and the courts have so held.

The second problem is the dependence on the drug firms to perform, direct, or arrange for testing drugs in which they have a financial interest. Again the drug firms are anxious to get new drugs on the market and to increase their sales volume. Drug testers are anxious to secure additional profitable contracts to test new drugs for the drug firms, and the accuracy and objectivity of some of these drug testers, the FDA has found, leaves much to be desired.

A physician who turns in unfavorable reports on drugs may not have his contract renewed. This type of environment is not conducive to the unbiased, objective type of drug testing which is absolutely necessary to insure that the public gets safe and effective drugs.

Today we will begin hearings on the drug indomethacin, which is manufactured by Merck under the trade name Indocin and, which is used in the management of rheumatoid arthritis. There is a question as to whether substantial evidence of safety and efficacy was available to warrant its release for marketing by FDA. In addition, there is an indication that the claims made by Merck for Indocin's merits were overstated and were made without the benefit of data gathered from accurate, scientifically controlled studies.

Our witnesses today will be Dr. William M. O'Brien, Department of Preventive and Internal Medicine, University of Virginia School of Medicine, and Dr. Donald Mainland, coordinator of studies—including drug evaluations in rheumatoid arthritis—conducted by the American Rheumatism Association Cooperating Clinics Committee. Tomorrow, we will hear testimony on this same drug from Dr. Robert S. Pinals, senior physician at the Lemuel Shattuck Hospital and assistant professor of medicine at Tufts University School of Medicine, Boston, and Dr. Gerald P. Rodnan, professor of medicine, University of Pittsburgh School of Medicine, and editor of the Bulletin of Rheumatic Diseases. On May 1 and 2, continuing our inquiry into indomethacin—Indocin-Merck—our witnesses will be Dr. Herbert Ley, Director of the Bureau of Medicine, FDA; Dr. Robert McCleery, Acting Director, Division of Medical Advertising, FDA; Mr. William Goodrich, Chief Counsel, FDA; and other members of FDA medical departments.

On May 3 we will hear testimony from the Merck Co. itself on this drug.[1]

Our first witness is Dr. Donald Mainland. Dr. Mainland, the committee welcomes you here this morning and appreciates your taking the time to come here to present your testimony. Your biographical background will be printed in full in the record as will the text of your statement. You may present it as you see fit and at any place in the statement that you wish to elaborate on your prepared text, feel free to do so. I trust that you have no objection to committee members interrupting your presentation with questions during the course of your testimony.

(The biographical sketch of Dr. Mainland follows:)

CURRICULUM VITAE OF DONALD MAINLAND

Born, England, 1902. Graduated in Medicine, University of Edinburgh, Scotland, 1925. D.Sc., University of Edinburgh, 1931. Guest research worker in the laboratory of the biological statistician, R. A. Fisher (later Sir Ronald Fisher) during summers in the 1930s.

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[1] Testimony for May 2 and 3, 1968, appears in "Competitive Problems in the Drug Industry, Pt. 8."

Fellow of the Royal Society of Edinburgh, Royal Society of Canada, American Statistical Association.

Demonstrator of Anatomy, University of Edinburgh, 1925–27. Assistant Professor of Anatomy, University of Manitoba, Canada, 1927–30. Professor of Anatomy and Chairman of Department, Dalhousie University, Canada, 1930–50. Professor of Medical Statistics, New York University, 1950 to date.

Coordinator of the studies of the Cooperating Clinics Committee of the American Rheumatism Association since its formation in 1958.

Member at various times of committees of the National Research Council of Canada, the National Research Council of the United States, the National Institutes of Health, Bureau of State Services and Veterans Administration.

Present spare-time occupation: preparation of notes and printed articles on medical research design and analysis for distribution by the Veterans Administration to its own research workers and to other investigators in the U.S. and foreign countries.

Principal research: mammalian histology and embryology, quantitative methods in hematology, X-ray studies of child development and of aging in adults, analysis of clinical and laboratory investigations, design of clinical experiments.

Ninety-five journal publications, a textbook of anatomy and two textbooks of medical statistics.

Member of various medical and scientific associations, including the British Medical Association, the American Rheumatism Association and the Biometric Society.

STATEMENT OF DR. DONALD MAINLAND, COORDINATOR OF STUDIES CONDUCTED BY THE AMERICAN RHEUMATISM ASSOCIATION, COOPERATING CLINICS COMMITTEE, NEW YORK, N.Y.

Dr. MAINLAND. Thank you, Senator. I should like at first to add a little bit more detail to the first paragraph of the prepared statement that I sent in advance and brought with me in large numbers today.

Under the heading "Speaker's Background," I graduated in medicine from the University of Edinburgh in 1925, doctor of science at the same university in 1931. I started teaching and doing research, teaching anatomy, and doing laboratory research immediately after graduation, and from 1927 to 1950 I did that in Canada.

The method that I used in the researches, various types of researches, some animal work, some tissue work, and some on human beings, they were the methods of experiment design and data analysis that are now accepted with appropriate modifications of standard methods for evaluation of drugs on human beings.

From 1950 onward I have been at New York University, consultant in clinical research, including drug studies. My title, by the way, is "Professor of Medical Statistics."

Since 1959 I have been the coordinator of studies, drug evaluations, and other investigations, in rheumatiod arthritis conducted by the American Rheumatism Association's Cooperating Clinics Committee, which now consists of 14 university-connected clinics throughout the United States selected because of their high quality of research.

I perhaps should point out that my full-time salary I receive from an NIH grant for this program of the rheumatic diseases group which is paid to New York University and then to me. I do some spare-time work for VA in consultation, mostly writing on methods of research and analysis. And, I receive no payment from any commercial organization.

Senator NELSON. You comment later on the funding of the American Rheumatism Association's Cooperating Clinics Committee. I believe NIH has provided the support; is that correct?

Dr. MAINLAND. Yes. NIH grant, a research grant.

Senator NELSON. And, there are 14 university-connected clinics that are cooperating in this particular program?

Dr. MAINLAND. But not always in every study. They were not all 14—at the time the indomethacin was done, there are, if I remember rightly, 11 clinics, I think. But now it consists of 14.

Perhaps I could expand on that question, Senator. The grant goes to New York University. It is the official applicant. And we in the coordinating center look after the grant. I am called the principal investigator. That is the mechanism. And then, we pay out from the university funds through their finance department the expenses in the various clinics.

Senator NELSON. Are the clinics who conduct investigations on any particular project required to submit their proposal for what they are going to do, or do you direct them as to what to do?

Dr. MAINLAND. They form the committee. The clinic chiefs or other senior people who are going to be responsible, they are the committee and they decide what they are going to do, and then they go home and do it.

Senator NELSON. Then, they submit the results of their clinical studies to you?

Dr. MAINLAND. To us, yes. And this is, of course, daily. We are receiving daily, or every few days, information. It does not pile up until the end of the study because we receive it, we check it, and make inquiries about the obscurities—anything that is not clear—and get an answer back, and then we accumulate all this information.

Senator NELSON. And this particular group is concerned only with rheumatic diseases?

Dr. MAINLAND. Yes. The rheumatic diseases. We have confined ourselves to rheumatoid arthritis up to the present but we do not eliminate the possibility of doing other studies in related diseases.

Senator NELSON. You have limited yourselves thus far to rheumatoid arthritis?

Dr. MAINLAND. Thus far, right. Could I perhaps continue with that particular indomethacin trial? The cooperating clinics committee—CCC—the 3 months trial of indomethacin in rheumatoid arthritis of limb joints. Technically we call it peripheral rheumatoid arthritis. It is the limb joints. There is a report published in the Journal, Clinical Pharmacology and Therapeutics, volume 8, 1967, pages 11–37. I have, I am sorry, only a limited number. I have six of the reprints here. Most of them have already been distributed to investigators and the committee. But, these are available.

Senator NELSON. This is the study you furnished to the committee?

Dr. MAINLAND. That is the study.

Senator NELSON. That will be printed at the conclusion of your remarks in the record.[1]

Dr. MAINLAND. This is the reprint. A complete report on this indomethacin study. I think it is perhaps important to notice the attitude of the committee at the outset. Without questioning the possibility that indomethacin benefits some patients, the committee wished to find evidence of the magnitude of the difference in outcome between a group of patients treated with indomethacin in customary doses—rising from 50 mg. to 200 mg. per day—and a comparable group of placebo-treated patients. That placebo was a variety of sugar and the drug and placebo were in capsules, so that they could not be distinguished from each other.

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[1] See article beginning at p. 2779, infra.

It was felt very important that a blindfold trial should be conducted; that is, one in which neither the patients nor the investigators know which treatment any particular patient is receiving.

All the patients were permitted to take aspirin, because deprivation of aspirin for more than a few days is not feasible with outpatients. It could be done in hospitals. They could be absolutely refused aspirin if they were retained in a hospital. Frankly, I do not think the committee would like to do that because we are concerned with human beings, patients, and we do not look on them as experimental animals.

It would not be feasible with outpatients. They would just take the aspirin anyway. And also this would not represent the way in which indomethacin or any other drug in rheumatoid arthritis would be given in practice. We wanted to reproduce that condition, and, therefore, aspirin was permitted, and most of the patients took it in varying amounts.

The comparison, therefore, was not between indomethacin and nothing, but between indomethacin plus aspirin and placebo plus aspirin. Some technical details to show the information are desirable. Monthly assessments were made. Methods were as far as possible, objective. They included the following: Numbers of activity joints; that is, painful or swollen. Grip strength—by squeezing a rubber bag as in blood pressure measurement. Duration of the morning stiffness that is present in many rheumatoid patients on awakening in the morning. The time required to walk 50 feet. There was also a special blood test called the erythrocyte sedimentation rate.

These methods seems crude compared with studies of certain diseases where one has very precise laboratory tests, to find bacteria, and so on. To ourselves, the methods look pretty unsatisfactory in one sense, but that is what we have available in rheumatoid arthritis—in the examination of the patients. In longer term studies, X-rays are available, of course, but during 3 months there would be expected no X-ray improvement with indomethacin or aspirin or any of those drugs.

Now, there was also used what is called the American Rheumatism Association scheme of functional classes. It is a four-class scheme to assess the patient's ability to perform his usual occupational duty. There were also used the patient's general impression of improvement or deterioration since the previous examination. That is, at the end of each month he was asked how he felt in general regarding his arthritis compared with the previous examination. And the physician's impression was recorded in the same way.

Those impressions are spoken of, and often criticized by some people, as subjective. The point here is that the impression of a patient and the impression of the physician are valid measures if nobody knows what agent, drug or placebo. the particular patient is using. It is a very important distinction. These can be criticized by some people who want to diminish the importance of value of any study by saying these are subjective patient feelings. That is not the point. The point is they would not be valid if the patient or doctor or nurse, for that matter, who could sort of encourage the patient, knew what the patient was receiving.

The duration of the trial: November 11, 1964, to September 8, 1965. Number of patients: They began with 136, about equally split between the drug and the placebo, and before the end of 3 months, 27 patients withdrew because of adverse symptoms or lack of improvement. That left 109, again in approximately equal numbers on the two treatments. Sex ratio was as usual, two to three females for every male. All patients were over 16 years of age and there was a wide range of ages, duration of the disease, and degree of severity at the beginning of the trial. That was similar to what had been found in one of the committee's previous studies on 499 patients.

The committee is not only concerned with drug testing but studying the disease and methods of assessing it, and it made a study, a systematic study, of 499 patients. The point I am trying to make is that because this much smaller group in indomethacin was quite similar to the 499 in its various features, we think that is a reasonable evidence that the indomethacin group were representative of the clinics.

Senator NELSON. What that study of 499 patients also a double-blind clinical test?

Dr. MAINLAND. No. We were not considering drugs. We just wanted to see how many joints they had painful, et cetera, and what their grip strength was, just what the condition was.

Two methods of analysis were used in the indomethacin study: Percentages of cases that were improved in the two groups and percentages of the cases that were deteriorated in the two groups in the various measurements, such as what percentage had more joints painful or fewer joints painful in the indomethacin group as compared to the placebo group.

The other method was measurement of rates of change; for example, so many fewer joints painful per month, so much increase in grip strength per month over the 3 months.

Regarding the percentages of improvement, that is, the percentage of cases improved, looking at all of them together, both the placebo and the indomethacin group, we found that the percentage of improvement ranged from about 35 to 50 percent in the different measurements that I mentioned, with very small differences in favor of the drug in some measurements and in favor of the placebo in others.

The average rates of change were very small in both groups. For example, there was an average change in both groups of less than one active joint per month. We looked also at the more extreme improvements—for example, 3.6 joints per month improved in the placebo group, 2.9 joints in the indomethacin group—slightly less but not really different.

In some measures, these differences, placebo versus drug, were slightly greater in the drug group and in others they were slightly greater in the placebo group.

With regard to functional classes that I spoke of, the functional classes of the American Rheumatism Association, the grading of their ability to carry on in their ordinary occupation, from complete ability, class I down to class IV, in which they are bedridden—in that classification we could see no distinction between the changes in the placebo and the drug group.

The impressions by physicians and patients of the overall change in the disease showed the following scores for improvement: The physicians reported 37 percent improved in the placebo group and 36 percent in the drug group. The patients who, unknown to themselves, were on the placebo reported that 48 percent had improved, and in the drug group 51 percent reported during the course of the trial that they had improved. There is essentially no difference between these percentages.

There was one clear-cut difference in the two treatment groups and this appeared in the week following the withdrawal of the medication. For 1 week after the end of the 3-month period still nobody knew which patients had received which medication. Patients and physicians were still blindfolded but both reported their overall impressions which showed a greater deterioration in patients who had been on the drug, but had now been taken off it, as compared to the placebo patients.

We could not explain that. We just recorded it.

The only objective measure that seemed to reflect this difference was that, in the patients who had been taken off the indomethacin as compared to those taken off the placebo, a few patients who had been on indomethacin showed rather marked increase in the duration of morning stiffness.

In all the analyses, attempts were made to see whether patients with different duration of disease or severity of symptoms at the beginning of the trial showed differences in response to the drug and placebo. We saw no such distinction. That is, we could not sort out future patients and say: "You will probably do well on indomethacin and you will not." We saw no suggestion of that kind.

The general conclusion of the committee can be summarized thus. In patients of this type, the type of which we are speaking, treated and examined as in this trial, with aspirin permitted to all patients, there seemed to be little to choose between indomethacin and placebo.

That summarizes their conclusions regarding the benefit.

I come now to undesirable signs and symptoms. On each visit, a query was made about the occurrence of 20 different signs and symptoms—for example, headaches, gastric distress, dyspepsia, dizziness. They are all listed in the printed report. Some patients at the very beginning reported headaches and what we wanted to do was see, during the trial, among those who had not had a particular symptom at the beginning, how many reported that symptom one or more times during the trial. These results were analyzed, symptom by symptom.

The only appreciable differences between the two treatment groups were in headache, dizziness, and lightheadedness. These were about twice as frequent on indomethacin as on placebo. As an example, headaches were reported by 32 percent of the placebo group, whereas 56 percent of the indomethacin group reported headaches. There was little difference in regard to gastrointestinal upset.

I should point out that none of these symptoms were serious and even in the patients who before the end of the 3 months had withdrawn because of disagreeable symptoms, none of the symptoms were at all alarming. That we reported as factual information from these 100-odd cases. We are not thereby implying what we think about the risks from indomethacin at all. We are just reporting.

It was suggested that I give some attention to the matter of the impact of advertising and promotional activities. I am not sufficiently acquainted with this topic to discuss it in general, but I have been interested in looking at one part of the evidence on which the producers of indomethacin have placed rather strong claims for the drug in rheumatoid arthritis of the limbs, peripheral rheumatoid arthritis; namely, the reports of a particular investigator.

In this month, April 1968, I received a production circular from the company that manufactures indomethacin, and I noted that there was mentioned in its list of references only one report by that investigator, one report on the use of the drug in peripheral rheumatoid arthritis. It was published in a certain journal in 1964 and it was a half-page abstract of a paper delivered at a meeting of a scientific association.

Mr. GORDON. May I interrupt here? In which journal did it appear?

Dr. MAINLAND. That journal name I can give you. I could give you the specific reference but not immediately. It was in Arthritis and Rheumatism, an abstract.

Mr. GORDON. Perhaps you can submit it to us later.

Dr. MAINLAND. I can supply it later. The report was by Dr. Smyth and others. I am not trying to pinpoint people here and I may refer to an investigator without naming him, because I do not want to point my finger at specific investigators, but I am quite willing to furnish the information desired.

(The information was subsequently received and follows:)

[From Arthritis and Rheumatism magazine, June 1964]

THE TREATMENT OF RHEUMATOID SPONDYLITIS WITH INDOMETHACIN

(By Charley J. Smith and Robert Godfrey, Denver, Colo.)

Indomethacin [1-(p-chlorobenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid] is a new non-corticosteroid agent with marked anti-inflammatory activity which has been employed in the tretment of various connective tissue disorders.

At the University of Colorado, 130 patients have received this drug during the past two years; extensive toxicity studies of hemotological, renal, hepatic and other metabolic functions have shown no serious toxicity reactions.

A critical analysis of 12 patients with rheumatoid spondylitis treated with this agent will be presented. Clinical response as reflected by both measurements and subjective criteria indicate that this drug has a prompt and striking beneficial effect. Dosage ranged from 100 to 700 mg. per day usually given in decreasing amounts over an initial period of two to three weeks with maintenance dosage of 100 to 200 mg. per day for up to 18 months. Objective measurements included chest-expansion, finger-tip to floor distance and walking time.

This presentation will include a short motion picture illustrating the dramatic change in "before and after" status of four of these patients with typical rheumatoid spondylitis.

Dr. MAINLAND. Now, that half-page abstract appears quite impressively in favor of the drug as one reads it, but papers presented at association meetings often appear impressive. They are interim reports presented for criticism by the audience and also to give the investigator a chance to establish a claim to a discovery if it should turn out to be a valuable discovery.

When a full report of that investigation was published the following year, 1965, the evidence was not nearly so impressive. In the most important part of it, the comparison of placebo and drug-treated patients, there was a serious flaw. I did not find that full report mentioned in the company's drug circular, but the circular contains the note: "Effective December 1967," that is, 2 years after that full report had appeared.

Now, I do not want to blame the drug company for using the evidence from the abstract. The abstract is printed public property. It could be used by anyone.

Even if the abstract had been read by experts in a drug licensing agency, they could not have detected that flaw I spoke about. I think they would have been impressed by the evidence presented in that half page and by the reputation of the investigator. Perhaps, and I am inclined to think this is so, the only way to stop this kind of thing is for a licensing agency to refuse to accept abstracts as evidence. Perhaps it might also frown upon the use of abstracts in drug publicity.

Now, I was asked to speak a little about safety and efficacy. Later on I would like to speak a little more in general about those topics but here, tying myself more specifically to indomethacin, I defer to Dr. O'Brien for an overall judgment regarding safety and efficacy of this drug because he has made such an extensive survey of that subject. But for what it is worth, I will mention what I personally, if I were in clinical practice, would be inclined to do if I had a rheumatoid patient who could not tolerate aspirin.

Because of a widespread impression among physicians that in some patients indomethacin does seem to help, and also because of that greater deterioration that we observed after these patients had been removed from indomethacin in the cooperating clinics' trial, I would be inclined to give indomethacin in preference to other commonly used drugs, but I would watch carefully for adverse effects.

I would like now to pass, if I may, to some general comments. It appears to me that while the main purpose of this subcommittee may be the protection of the public in an economic sense, when the subcommittee is concerned with problems in the field of drug production, it is playing a very significant role in the field of health care, and this is a very complex area. Even solely concerning the evaluation of drugs, it is a complex area, and it has occurred to me that perhaps the subcommittee would find something of interest in a few comments by one who has been in the field of drug evaluation since the beginning of what one can call the modern period, and that is about 20 years ago. I have been in it all that time, and my comments may be of some interest.

The modern period of drug evaluation we can say is the period when medical people have come to recognize more and more that the only really reliable way to evaluate drugs is by the controlled trial. The essence of a controlled trial is that one drug is used on one group of patients and concurrently, at the same time, there is another group which is called the control group. That is technically a controlled trial—a control or contrast group of similar patients, handled in the same way as the drug treated, except that this other group receives either another drug or receives a placebo.

Further, the observations must, if possible, be made blindfold. Neither the physicians nor anybody connected with them or the patients have to know which treatment any particular patient is receiving.

Now, if blindfold methods are impossible, and that is so in testing of certain drugs, the observations must be made in such a way as to exclude the risk of bias and there must be systematic observations, and the observations and methods of observation must be the same for both groups. That is a sort of thumbnail sketch of a controlled trial.

I would like to add this, that although by nature I am not an optimist, when I look back 20 years I am greatly impressed by the progress that has been made in the understanding of the need for controlled trials, not only in the medical profession but among intelligent members of the public. I suggest that perhaps the members of the subcommittee who find so many wrongs to be righted may also perhaps occasionally be encouraged by this progress. This does not at all imply that we should be complacent, not at all, but improvement has occurred and, by effort, much greater improvement obviously can be made.

A word about experiments. We do not use the word "experiment" in our discussion of these trials. We call them trials because experimenting on human beings has a very bad sound. It sounds as if controlled trials are experiments on human beings in the sense of using those people not for their own benefit but for the experimenter's purposes.

Those of us who know what actually goes on in a good drug trial—that is, a trial that is conducted by good investigators who are also good doctors—we see the matter differently. An important point that many people do not realize is that every time a doctor in the ordinary course of his work tries a drug, even a much used drug, on a patient for the first time he is performing an experiment. It may do the patient no good and, with most of the powerful modern drugs, it may well do him harm.

If I were a patient, I would much prefer to be in a good experiment, that is, a good drug trial, even taking a 50–50 chance of a placebo, because I would receive more thorough and systematic examinations than can possibly be given to routine patients. And I would know that, in a double-blind trial, neither I nor the doctor have been fooled by knowing that this was supposed to be a miracle drug. And, I would know that, if things were going wrong, I would be taken out of the trial.

A word about pharmaceutical companies. The executives of the pharmaceutical company may, as individuals, be altruistic. I have met, over the years, a number of them, and I feel they are basically altruistic individuals. I know some of their scientists and often they are of high quality, but we should never forget that the primary aim of a company is commercial. A company can make a quick million or two out of a new drug that is subsequently found to be of no particular value.

Now, some of the more enlightened companies are coming to realize that a succession of those things, a succession of these flash-in-the-pan drugs, does not build a good reputation. We may hope for the spread of such enlightenment, but in the meantime, we should, I think, ask what can be done to counteract the influence of the marketplace in drug evaluation.

It seems to me that the most obviously desirable step would be to take the evaluation of drugs entirely out of producers' hands.

Senator NELSON. May I interrupt for a moment?

Dr. MAINLAND. Surely.

Senator NELSON. Would you care to elaborate on what method of evaluation you would propose be followed if the evaluation of drugs was to be taken out of the hands of the drug company itself?

Dr. MAINLAND. Yes.

Senator NELSON. I take it you are talking about the evaluation for purposes of submitting a New Drug Application to FDA? Is that what are talking about?

Dr. MAINLAND. Evaluation in order to produce evidence that a scientific licensing organization, FDA or any other, would be able to accept and say, yes, the evidence is good. That is what I mean by evaluation, as we were evaluating indomethacin. I do not mean any preliminary evaluation. My proposal would be to take it entirely out of the producers' hands. May I, sir, postpone a little fuller comment on that to some later statement that I plan to make in this prepared document? [1]

Senator NELSON. All right. May I raise another question about that? I assume you are not suggesting that the companies that are producing the drug and doing the research should not carry on some experiments of their own.

Dr. MAINLAND. On animals they certainly should experiment.

Senator NELSON. On animals.

Dr. MAINLAND. Yes. I may be very radical—I am not a policymaker but that is my feeling, that this would be the most desirable step to get the marketplace out of the drug evaluation.

Senator NELSON. I know you are going to talk about this later, so I do not want to get into it, but we are, for purposes of the record, talking about the evaluation now done by the company in submitting its New Drug Application to the FDA for approval or disapproval?

Dr. MAINLAND. The definition of evaluation that applies here is the clinical testing of drugs. In general, the drug companies ask individual doctors "will you test this?" and they pay them, quite frequently pay them for the testing. That should be taken entirely out of their hands, in my opinion.

Senator NELSON. So that when a New Drug Application does come to the FDA, what they would be looking at is an evaluation that has been done by some independent source not associated with the commercial enterprise of that drug company; is that correct?

Dr. MAINLAND. That is correct.

Senator NELSON. And, you will elaborate on that subsequently?

Dr. MAINLAND. Yes, and suggest some sort of possible mechanism.

Senator NELSON. All right.

Dr. MAINLAND. Perhaps there should be added at that point that am not referring to animal experimentation. There would be no very good reason for anyone who is producing a chemical not to do animal experimentation in his own laboratory. I am thinking about human investigation, investigation on human beings.

The attitude of the cooperating clinics committee is in line with that. The cooperating clinics committee when it conducts drug trials insists that after the manufacturer supplies the drug, he and his agents make no further contact with the investigator with regard to the trial. Any necessary communication between the drug house and the investigator has to come through the coordinator's office, through my office.

That has not been an easy achievement because FDA regulations regarding new drugs confer on the manufacturer the responsibility to produce evidence regarding the trial and safety of the drug. The company is the sponsor of the trial and the investigators are to communicate with the sponsor, not directly with FDA.

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[1] See supplemental statement of Dr. Mainland on "Substantial Evidence," p. 2778, infra.

Senator NELSON. But, the trials that you are talking about, say on indomethacin, were trials that had been conducted after the New Drug Application had been approved, after the drug was on the market?

Dr. MAINLAND. Yes. I refer specifically to new drugs here at this point.

Senator NELSON. I see. So, you are referring to a situation where there would be clinical trials prior to the approval of that drug by the FDA for marketing.

Dr. MAINLAND. Correct.

Now, theoretically, our committee, the cooperating clinics committee, or any other group of investigators, could be the sponsor of a trial. They could run their own trial and they could theoretically take the place of the pharmaceutical company in being responsible directly to FDA. I looked into that possibility very carefully and I found that we, the committee, would have to produce for FDA so much evidence regarding the drug, its chemistry, its animal experiment results and any previous clinical tests, and go through so many official steps, with the inevitable delays, that I decided to drop the idea of the committee being its own sponsor. This was not concerning indomethacin. It was another drug in which we had to get FDA permission.

Senator NELSON. There was a case where you explored the possibility of your group being the sponsor of the experiments required for the New Drug Application?

Dr. MAINLAND. That is right.

Senator NELSON. And you decided that because of the elaborate detail that must be supplied, it was not practicable for you to do it?

Dr. MAINLAND. That is right.

Senator NELSON. And, you will comment later on a suggestion that you think may make it feasible to have independent sponsors?

Dr. MAINLAND. Yes.

Now, as I said, we keep the drug companies out of our trials but even though the pharmaceutical company agrees to avoid contact with the investigator during the trial, the company can still claim its right under FDA regulations regarding new drugs, claim its rights to examine the data, to examine our analyses and our reports before publication. If a report were adverse to a drug, there is, so far as I can see, nothing to prevent a company introducing such delaying tactics that the investigators would get tired and the report might not be published at all.

In the meantime, another report by other investigators apparently more favorable to the drug could have been published.

I should like to say a word before leaving for the moment the matter of pharmaceutical houses. Both Dr. O'Brien and I in our statements do see very serious things that are wrong with the present setup but I should like to say from my own experience with the various companies that they have been very cooperative in providing the material, in making up placebos that really do imitate the drug, and in bottling and labeling according to our instructions. A colleague of mine commonly goes to the company's bottling plants to see that these are done correctly, and we have been made very welcome, although the companies have known that this was a double-blind trial and it might tell adversely on their product. At any rate, they have given us their cooperation.

The matter of support—financial support for drug evaluation. Good drug evaluation is expensive. In any large trials there have to be some full-time people in the coordinator's office. Clinical investigators who devote part of their time to a drug trial have to receive some payment. A good part-time secretary is necessary, absolutely necessary, at each clinical center. Then, there are laboratory costs, X-ray costs, and so forth.

Much of the money, of course, at present for drug evaluation goes directly from pharmaceutical houses to the clinical investigators. The cooperating clinics committee is very much opposed to this. It accepts the drugs without paying for them but it will accept nothing else from the drug company, not even a free lunch.

Senator NELSON. Speaking about the cost of a good clinical study, do you have any careful breakdown that would demonstrate cost? For example, how much did it cost to conduct the double blind trial that you conducted with indomethacin?

Dr. MAINLAND. Indomethacin? There is a little difficulty in separating costs out because we run several studies—they are not always drug studies—at once, but we feel pretty close to the figure when I say that the total cost, including the clinics and central office, was $51,000 for the indomethacin trial.

Senator NELSON. That was the 1-year trial on 136 people, was it not?

Dr. MAINLAND. Yes. That was from November of one year to September of the next, and the number of patients was 136.

Senator NELSON. What is the cost factor involved with the cooperating clinics committee? What do you pay them for?

Dr. MAINLAND. We pay them for laboratory expenses which are generally—as a matter of fact, nearly always—below the ordinary routine charges in the treatment of patients. We pay not at all handsome fees to the clinicians who do the investigation. X-ray costs, half the usual price quite often. Postage, mailing, secretarial salary, part time, maybe sometimes 2 days a week, sometimes more, sometimes less. Those are the clinic charges. Transportation. In difficult cases we have permission from NIH to pay transportation for patients who for various reasons would not attend.

Senator NELSON. Would you have considered the double-blind trial that you conducted on indomethacin with your cooperating clinics committee to be an adequate trial to support a New Drug Application? Or, in other words, based on the trial you conducted, if that was the total information that was available, would you think the FDA ought to approve this drug to go on into the marketplace as meeting the requirements of the law for safety and efficacy?

Dr. MAINLAND. This is an imaginary case in which only this evidence from this trial was available in the whole world. Is that right?

Senator NELSON. I am assuming that results of animal experiments were available but that this was the sole evidence available on human experimentation.

Dr. MAINLAND. Yes. Oh, I would not think that that was adequate to permit the drug to be by itself.

Senator Nelson. You would not think that was adequate?

Dr. Mainland. No.

Senator Nelson. Was the evidence that was submitted by the company at the time of the New Drug Application more adequate than what your experiments demonstrate?

Dr. Mainland. I would have to defer to Dr. O'Brien for an answer to that. My experience refers to the deterioration in some patients after our trial, and there was an English trial—a double-blind trial—that did seem to show that the patients felt somewhat better, had more energy on indomethacin, but it was not a very objective thing.

Let me try to think what my feelings would be if I were a member of a licensing board. That is, I guess, what you would like me to do.

I am sorry. I really cannot answer that question. I am so doubtful as to whether I would or would not feel that it was desirable to permit the general use of the drug. I think I will put it this way, that it had seemed to show some benefit in some patients and that with care it might be very cautiously tried. I am in a quandary. You cannot restrict physicians from doing it carelessly when there is not clear evidence in favor of it. I am puzzled.

Senator Nelson. As I understand the results of the clinical testing you did, the placebo and aspirin and the drug and the aspirin, produced for all practical purposes exactly the same objective result as far as you could determine with the methods of measurement that you now have respecting rheumatoid arthritis.

Dr. Mainland. Right.

Senator Nelson. Therefore, as to peripheral rheumatoid arthritis, you did not produce, as I interpret your experiments, any objective evidence of a greater efficacy on the part of the drug and the aspirin than on the part of the aspirin and placebo, is that correct?

Dr. Mainland. Right.

Dr. O'Brien. I would just make a point, Senator Nelson, that under the present legislation I do not believe it is necessary for the companies to show that their drugs are better than drugs presently on the market, and if Merck had shown that indomethacin was as effective as aspirin, under the present legislation it could be marketed.

Senator Nelson. But as to this double-blind trial, aspirin was used in both cases and aspirin and placebo produced the same result as aspirin and the drug. Therefore, what is the evidence in that trial of the efficaciousness of the drug when added to aspirin? As I understand it, there was no objective evidence of additional efficacy, is that correct?

Dr. Mainland. That is right. That 1-week posttrial, that was the only thing that seemed to show, because some of the patients felt worse who had been taken off the indomethacin, proportionately worse than those who had been taken off placebo, but that is a feeling. It is not objective evidence.

Senator Scott. Would you say, Doctor, that this might indicate after the withdrawal that there is a faster return of the disease symptoms?

Dr. Mainland. After withdrawal from the drug as compared with withdrawal——

Senator Scott. As compared to the withdrawal from the placebo.

Dr. Mainland. Yes. A faster return. As I said, we just recorded it. We did not know what to make of it. We just simply recorded it.

Senator SCOTT. After all is said and done, after all of the testing, you do say in your statement that if you were a clinician, and you had a rheumatoid patient who could not tolerate aspirin, because of a widespread impression that indomethacin helps some patients and because of the greater deterioration in some patients in the CCC trial after the drug had been withdrawn, you say in your statement that "I would be inclined to give indomethacin in preference to other commonly used drugs and I would watch carefully for adverse effects."

Now, is this conclusion after all basically any different from that which the drug company itself is seeking to ask physicians to draw using the normal care which physicians are expected to use? In other words, you are more of an expert than the average prescribing physician and you come to a conclusion that you would use it under certain circumstances.

Dr. MAINLAND. I would give it a chance. I would not be surprised if it failed.

Senator SCOTT. That, of course, is what every physician does, as you say in your statement, every time he prescribes a new drug for the first time to a patient. He would not be surprised if it failed. He is trying to find out, is he not?

Dr. MAINLAND. Yes; with regard to the reference to how the information or the inducement, shall we say, is presented by the company, they could not sell drugs on my form of advertisement. I do not think they could sell much on the basis of what I would say that there is an impression and I would be inclined to try it, but that would not sell a drug. That is not the way they phrase it. I think it is the exaggeration that I am perturbed about, the exaggeration in the advertisements.

Senator SCOTT. In the 11-clinic study as I understand it, both the test group and control group were allowed all the aspirin they wanted? That is, there was no limit to an outpatient. Each one could take whatever aspirin he wanted to dose himself with, could he not?

Dr. MAINLAND. Yes.

Senator SCOTT. And, that being the case, if aspirin is effective, how, then, can you really measure the real value of another drug when all patients in both the P and the D groups are taking aspirin? Might it not be the aspirin which helps or fails to help in any event?

Dr. MAINLAND. Oh, yes. That is so. The question is, Did indomethacin show up as doing something more under those conditions because these were the natural conditions?

Dr. O'BRIEN. Also, Senator, the number of aspirin tablets consumed were used as a measure of the effectiveness of the drug or placebo and the number of aspirin tablets consumed in the drug group and placebo group were not significantly different.

Senator SCOTT. The aspirin itself can have some side effects, can it not?

Dr. O'BRIEN. Yes.

Senator SCOTT. I am sitting right here now with some side effects of aspirin. That is why I am sure that I am right on this.

Dr. Mainland, obviously, we need the most careful drug evaluation we can get in this country. What alternatives would you suggest to the present systems of drug evaluation, bearing in mind what the companies do and what the Kefauver Act prescribed? Do you have other alternatives to suggest?

Dr. MAINLAND. Yes; I have given thought to this matter. I am not an expert on policy matters and I do not know about the practical feasibility of things, but I visualize some sort of a drug-testing agency or organization, not a governmental department, and certainly not run by the drug companies. I have written a few notes which are not in this prepared statement, subsequently written, to this effect, that this agency, this effort involved in the evaluation, should attract the best investigators in the country who want to do this kind of work. It should not be a commercial organization. It is something in my mind like the scheme of NIH in regard to its grant-awarding sections. I am not talking about contracts but about grants, research grants. That is, there is a council of experts. I can visualize a council of experts, perhaps several divisions of it, not government employees, but from universities and, shall we say, similar institutions. The council, as I picture it, would invite senior investigators of various centers to form working parties for individual drugs. I am using the words, "working parties" partly because I have in mind also the English Medical Research Council. Perhaps I had better postpone that point because there is a close analogy in a way, between that and the NIH setup for grant work.

These working parties would choose suitable investigators, less senior than themselves, although some of the top clinic chiefs in our cooperative studies do the actual investigations themselves; but in general this would be the setup, that they would choose less senior investigators to carry out most of the work but they would be carefully chosen.

The point I would like to stress is that this should be only part of these people's work. I do not visualize an organization in which people who work for a group, by its support, do nothing but drug testing. This should be only part of these people's work. If these people who are not quite at the top of the ladder want to rise in their profession, this kind of activity will not help them very much. It does not help anyone very much to have his name along with 20 or 30 other investigators as having participated in drug trials.

I can visualize quite a lot of difficulties in this.

Another point I might stress is that the terms of reference and the financial aid to be flexible. Now, in a current trial I am engaged in, another drug, it was planned to do a certain test once every 2 weeks. After the trial had started, information came from outside the trial, from investigators who were acquainted with this drug, to show that it would be desirable to do this test once a week instead of once every 2 weeks. I made a rough estimate, at, say, $5 a test, this would be about $50 per patient. For 100 patients, it would be $50 times 100, which is $5,000. By the way, we are doing that extra test. I am not saying these figures are exact for our expenses but that is the proper rate. On our grant this means that we have to cut out some other part of the program. We would not cut anything out of that trial but certain other parts of the program. Or we might say, well, we have not enough money left to start another drug. But still we can do the test. We are doing it. We are adding that weekly test instead of the every 2 weeks. But you set limitation under a set amount on the grant.

It would be much worse on the contracts which I am aware of, and I have worked with them; for example, one was in cancer chemotherapy. This situation would then be much worse. This item, this extra test, would not be in the contract and we would have to get special permission and special extra allocation and this might take weeks or months and in the meantime the patient might be running unnecessary risks.

I am trying to visualize more specific mechanisms than just the general statement that there would be a council.

With regard to financial support of this visionary or imagined organization, the taxpayer might be expected to contribute a little, but I am not even sure of that. I am not competent to talk about the economics in detail. The people who are going to benefit most financially from approved drugs are, of course, the drug companies, but contributions from them should be done by putting their contributions into some central fund and there should be no strings attached. The arrangement should be that they could not influence the disposal of the money or interfere in any way with the trials or with the results.

Senator SCOTT. Do you have any idea at this time, Doctor, of how much money is presently being expended annually by the drug companies in the experimentation and evaluation of new drugs?

Dr. MAINLAND. I think Dr. O'Brien might have some general figures on that.

Dr. O'BRIEN. The drug industry, I believe, lists its research expenditures as somewhere around $470 million. A great deal of this is for basic development pharmaceuticals which is not pertinent to what we are talking about here, which is clinical testing of drugs.

Now, the amount of money spent on clinical testing of drugs in the United States is very difficult to work out. I inquired of several centers trying to determine this. The National Institutes of Health has earmarked for expenditures on pharmacology somewhere around $45 million. Of this, only $3,500,000 is specifically earmarked for clinical testing of drugs by independent investigators. The drug industry has set aside some funds for independent testing of drugs by investigators who are uninfluenced by the drug industry. Two good examples of this are Burroughs Wellcome, which funds clinical researches, and now Hoffmann-La Roche has set up an independent research organization. Lilly has for some years funded an institute to test drugs but these are few and far between. At the present time, the Pharmaceutical Manufacturers Association is spending only $107,000 per year funding this type of work which, incidentally, is less than the budget of our cooperating clinics committee. The Association of American Medical Colleges estimates that medical schools receive somewhere in the vicinity of $3,100,000 per year as gifts from nongovernment sources for independent research. Of this, I would guess probably at least half comes from the drug industry. The budget for research in medical schools runs somewhere around $375 million per year according to the Association of American Medical Colleges, so less than one-half of 1 percent of the total research budget of the medical schools comes from the drug industry.

The pharmaceutical industry indicates that this figure is much higher—about 2 percent of their research and development expense. However, some of this money is going to physicians who have appointments in medical schools, but the money does not directly come into the medical school and is not directly administered by the medical school. I would say these funds are being directly used to support medical schools. Thus, I think the amount of money for independent clinical research on drugs available in the United States right now is very limited. The main source of funds for this is the National Institute of General Medical Sciences of the National Institute of Health.

Senator SCOTT. Well, let me ask Dr. O'Brien, then, how much money would you expect it would take to conduct independent clinical research of this type if this function were taken away from the drug companies and conducted by some other group?

Dr. O'BRIEN. Well, I think a better person to talk about this would be someone from the NIH, but for specifically funding clinical pharmacology in America's medical schools, I would estimate that it would take around $50 or $60 million a year at least to take over this function and I think this is considerably cheaper than the cost of doing medical research on clinical testing of drugs right now. It is done in a rather haphazard fashion with small funding, many, many investigators of questionable quality.

Senator SCOTT. If you were to take over this function from the drug companies, with their presumed consent, would you not then remove from the drug companies all responsibility for putting their own guarantees behind the sale of the drugs and turn them simply and purely into the commercial aspect of their work—that it, the distribution for a profit of the drugs—without any requirements to put any kind of backing behind it except a statement to the general effect that their drug had been examined and had been found effective by this independent agency together with what other safeguards were required in the statement to be made by the company? Would that be a good solution?

Dr. O'BRIEN. I would not have any quarrel with having the drug companies test their drugs independently and provide independent data, but it would seem to me that the problem is that the drug companies are testing their drugs and producing very highly biased results which indicate the drugs are far more efficacious and far less toxic than they actually are, and I think indomethacin is a case in point. The earliest statements on this drug indicated that it was a very powerful drug with very low toxicity and subsequent experience has shown this has not been true, and it is tests by independent investigators which finally demonstrated that the drug was nowhere near as powerful as thought, and it was considerably more toxic than was thought. I think this is the nature of the problem: Can we get unbiased evaluations by the drug companies because of the tremendous pressure of the marketplace?

Senator SCOTT. Does not the FDA have the authority to correct any inaccurate claims made by the drug companies?

Dr. O'BRIEN. Well, this is getting into my testimony, but as I tried to document in my testimony, I do not think the Food and Drug Administration is enforcing the present legislation.

Senator SCOTT. I understand—I would be very glad to have either of you gentlemen add some comments on this—it is rather an ad personam argument but an interesting one, I think—I understand the eminent heart surgeon, Dr. Christian Barnard, has publicly stated he uses indomethacin for the arthritic condition in his hands. He stated, "I have been using it for 3 years and frankly, I could not do without it."

Now, here is a physician—a very eminent one—who clearly thinks he needs it.

Dr. O'Brien. I think Dr. Barnard is a superb heart surgeon and technically his skill is admired by all of us. How good he is at managing drugs I would not know.

Senator Scott. He still nevertheless—what I am speaking of is how good drugs are at managing him and managing his hands——

Dr. O'Brien. Dr. Barnard has published a series of magnificent technical papers on various aspects of cardiovascular surgery. I do not think he has published a single paper or treated a patient with rheumatoid arthritis except himself and I would hardly accept him as an authority.

Senator Scott. But, you do not think it is at all important that Dr. Barnard feels better and feels that his condition is being improved because he is taking a certain drug? That does not have any impact with you at all?

Dr. O'Brien. None whatsoever. I do not think Dr. Barnard is qualified in doing clinical trials nor has he had any training or experience in treating rheumatoid arthritis.

Senator Scott. Dr. O'Brien, do you know Dr. Barnard?

Dr. O'Brien. No. But I am very interested in immunosuppressives and realize the pharmacologic problems that the surgeons face and I say that the technical skills required in surgery are quite different in pharmacology.

Senator Scott. Are you prepared to say that Dr. Barnard, in his general practice, has never treated cases of rheumatoid arthritis?

Dr. O'Brien. He may have seen some but I do not think he has ever systematically published on the disease or published anything. I keep up with the literature on treatment of rheumatoid arthritis quite well and I am unaware of any significant publications by Dr. Barnard in this field.

Senator Scott. But then, we can leave it that he may have treated rheumatoid arthritis cases.

Dr. O'Brien. He has been so busy doing heart surgery that it would seem unlikely but he may have, Senator.

Senator Scott. Well, I am grateful for small favors, Dr. O'Brien.

Dr. O'Brien. Shall I continue through this or is there any more questioning along this line?

Senator Nelson. I have a couple of questions.

Dr. O'Brien. I was going to speak about the research grant.

Senator Nelson. Dr. O'Brien, in the event that some independent group was established, such as the American Rheumatism Association Cooperating Clinics Committee, for the purpose of independent evaluation of drugs to be submitted to the FDA for its consideration of New Drug Applications, is there any reason why the companies themselves could not conduct both animal and human studies as they desired and submit their findings along with the independent agency? I raise that question because even now when the FDA takes issue with the company over a drug in the marketplace, as I understand it, under the law the company is personally entitled to submit experimental data to prove their point vis-a-vis a viewpoint of the FDA. I believe they have a right to do so under the law and I think they ultimately could go to court and might prevail in a dispute with the FDA over the validity of the experimental data they submit. My question is, is there any reason why they could not obtain the same kind of information, submit the data to FDA, while at the same time the FDA would have before it a double blind trial done by an objective independent agency? Is there anything wrong with that approach?

Dr. MAINLAND. I have been so familiar with the reports of varying qualities and so much inside research, clinical research, not only in drug tests, that I would not feel confident that I, receiving a report, if I were asked to help FDA to judge between a drug company's reports and someone else's, I would not feel confident that I could really detect flaws in a report that came from a drug company because in the work that I am familiar with, working with the investigators, not only in drugs but other things, they are really trying to be quite honest. They have nothing to sell. And even then, although they have been perfectly honest and objective, they can have overlooked certain potential biases and we have to go over the material again and again, probe and find out what is going on.

I am never satisfied, I might say, in regard to the individual investigators, I am never satisfied until I see what they are actually doing in the laboratory and, therefore, I can visualize a situation in which, receiving a report from a drug house on a certain drug, I can say, "Well, did you or did you not have controls?" Oh yes, they would say, "We had controls." These terms like controls and double blinds and objective, statistical analysis, more and more as we look into the literature, the more doubtful we become about the use of those terms by certain investigators. Looking under the label we can find defects and I really would not feel—this is my personal feeling—I would not feel contented that I had been able to detect flaws which had, shall we say, been introduced for purposes other than purely scientific objectives. That is my answer.

Senator NELSON. I was really getting at the question raised by Senator Scott about removing the companies from any kind of trials involving human beings and what the consequences of that might be. Now as of the present, there is no comparative data from an objective source that goes to the FDA along with the firm's New Drug Application. The application is developed by the company alone. It may be very good or it may be very poor. It may have a lot of bias in it or a little bias in it.

In the first place if the company data would be compared with data from clinical trials done by an objective independently funded source, would not that naturally incline the company to produce better information itself?

And, secondly, I am assuming that those who evaluate the application are qualified to make some judgments about the quality of the research presented to them and would be qualified to make a judgment about it, just as any judge in a court has two viewpoints presented to him by very able advocates and, based upon the competing ideas presented, he makes a decision.

Would you like to address yourself to that, Dr. O'Brien?

Dr. O'BRIEN. I think this is anticipating my testimony. I would defer it until then.

Senator NELSON. I just had one more point that I may have misunderstood prior to this issue being raised a while back. I thought I understood Senator Scott's question to say that after the conclusion of the administration of the placebo and the aspirin and the drug and the aspirin, those who had not been on the drug demonstrated some symptoms of discomfort, and so forth—I do not know if that was the way it was put.

Senator SCOTT. From the withdrawal. Those who had been on drug plus aspirin showed greater deterioration than those who had been on placebo plus aspirin. That was, I believe, the nature of my question.

Senator NELSON. Yes. That was not the way I understood the testimony here. On page 2 it reads:

> The only clearcut difference in the two treatment groups appeared in the week following the withdrawal of the medications at the end of the 3-month period. Patients and physicians were still "blindfold" but both reported their overall impressions of deterioration greater in patients who had been on the drug than in placebo patients—about twice the——

Senator SCOTT. That is what I said. And there it is again, in that portion of Dr. Mainland's statement under the subheading "Safety and Efficacy."

Senator NELSON. I misunderstood you. So, the findings are that the deterioration was greater after withdrawing the drug than it was after withdrawing the placebo.

Mr. GORDON. What is the significance of that?

Senator SCOTT. The significance of it to me at least, was in the testimony of Dr. Mainland that all these things being true, he would be inclined, if he were a clinician, to prescribe indomethacin in preference to other commonly used drugs.

Dr. MAINLAND. Only if these patients could not tolerate aspirin. That would be my last resort.

Senator SCOTT. With that qualification.

Dr. MAINLAND. Yes, and I would be thinking about the patient and when you are thinking about a patient you are not as objective as when you study reports. We never forget that.

Senator SCOTT. I must say as a patient I am glad to hear that.

Senator NELSON. Please go ahead.

Dr. MAINLAND. I think I was talking about the matter of the research grants support and I think I made it clear, the matter of the research grants support from the NIH, and this is in many ways a desirable form of support because by this mechanism the investigators must really want to do the research and then if their proposal is approved by panels of other scientists, outside the Government, their proposal stands a chance of being funded. The Government in this system does not produce the money to tempt people who would not otherwise wish to do drug evaluation. To one who is not interested, the detailed work is boring and then the quality of their work is not as good or there may be a good quality of work and then a drop. And then, of course, as with all research grants from the Public Health Service, the Government does not direct the research. The Government does not tell you specifically what to do.

Now, as I see it, the chief disadvantage of the Public Health Service research grant mechanism overall is the following: It concerns the matter of whether people get money or not. An application for a research grant support of a drug evaluation has to take its place in competition for often limited funds with applications for many other kinds of medical research and if a reviewing panel feels that these other things are more important than drug evaluation, a good proposal may get a low priority and not be funded.

It would seem that if the people, the public, really feels that good drug evaluation is important, there should be some more assured form of support and the funds available, whether from public or private sources, should be much larger than they are at present.

A word or two about the FDA. During recent years the activities of the FDA have done something to improve the standards of drug evaluation, but this has entailed certain disadvantages. I have reason to believe that in the personnel of the organization, there are considerable differences in scientific standing and in the understanding of these problems. I am not sure, for instance, that every senior staff member who has to make decisions about drug evaluation really knows what a controlled trial implies.

We may hope that the staffing situation will improve. There is, however, an impediment that is inherent in such a governmental organization, the effect of public opinion. The public is anxious to have more and more powerful drugs but it is concerned about the disastrous effects of some recent drugs and does not seem to realize that to satisfy its desire for more and more drugs, risks are inevitable. If something goes wrong with a patient even in a very careful drug trial, there is a feeling that somebody must be to blame and the natural place to fix the blame seems to be on a Government employee who has permitted the trial to take place. It is also natural, therefore, for such employees to try to avoid such risks.

I might briefly mention the case in which I was involved recently. A very experienced group of investigators proposed to test a rheumatoid arthritis drug that involved some risks. The drug had been used in another disease for a number of years and the investigators knew how to reduce the risks greatly. All this evidence was supplied to FDA. But, and this is my chief point, the responses from different equally authoritative officials were completely at variance, and it took some 6 months before an agreed verdict of permission was obtained.

What struck us particularly as interesting, was that since this drug is available on prescription, it is now being given to rheumatoid patients by some physicians without the precautions that the investigators proposed to take. So, while FDA was holding back a good investigation that would have stood a pretty good chance of answering the question of whether it was a very good drug or just fairly good or perhaps not particularly good or too dangerous, in the meantime. this particular drug is being prescribed to rheumatoid patients.

Now, I feel sorry for FDA officials under public pressure but it seems there is some room for improvement in the organization.

I am just looking through the other notes that I have added and perhaps the question of substantial evidence will come up later. I have some notes on the question of what one would call substantial evidence. But perhaps I should now defer to Dr. O'Brien.

Senator NELSON. All right. We will no doubt have some further questions of both you and Dr. O'Brien.

(The complete prepared statement, supplemental statement, and supplemental information submitted by Dr. Mainland follows:)

STATEMENT OF DR. DONALD MAINLAND, COORDINATOR OF STUDIES CONDUCTED BY THE AMERICAN RHEUMATISM ASSOCIATION, COOPERATING CLINICS COMMITTEE

The Speaker's Background.—After graduation in Medicine he conducted laboratory research (1930–1950), using methods of experiment design and data analysis that are now accepted, with appropriate modifications, as standard methods for evaluating drugs in human being. From 1950 onward he has been a consultant in clinical research, including drug studies. Since 1959 he has been coordinator of the studies (drug evaluations and other investigations) in rheumatoid arthritis conducted by the American Rheumatism Association Cooperating Clinics Committee (CCC), which now consists of 14 university-connected clinics throughout the U.S., selected because of their high quality of research.

The CCC Three-Month Trial of Indomethacin in Rheumatoid Arthritis of Limb Joints.—Report in *Clinical Pharmacology and Therapeutics*, vol. 8, pp. 11–37, 1967 (Jan.-Feb.). Without questioning the possibility that indomethacin benefits some patients, the Committee wished to find evidence of the magnitude of the difference in outcome between a group of patients treated with indomethacin in customary doses (rising from 50 mg. to 200 mg. per day) and a comparable group of placebo-treated patients in a "blindfold" trial, i.e., one in which neither the patients nor the investigators know which treatment any particular patient is receiving.

All the patients were permitted to take aspirin, because deprivation of aspirin for more than a few days is not feasible with outpatients and because it would not represent the way in which indomethacin or any other drug would be used in practice. The comparison, therefore, was not between indomethacin and nothing, but between indomethacin plus aspirin and placebo plus aspirin.

Monthly assessments were made. Methods were as far as possible "objective": numbers of active joints (painful or swollen); grip strength (as in blood pressure measurement); duration of the morning stiffness that is present in many rheumatoid patients on awakening in the morning; time required to walk 50 feet; a blood test (erythrocyte sedimentation rate). Also used were (1) "functional classes"—a four-class scheme to assess the patient's ability to perform his usual occupational duties; (2) the patient's impression and (3) the physician's impression of the patient's improvement or deterioration since the previous examination.

Duration of trial: November 11, 1964 to September 8, 1965. Number of patients: 136—65 on the placebo (P) and 71 on the drug (D). Before the end of 3 months, 27 (12 P and 15 D) withdrew because of adverse symptoms or lack of improvement, leaving 109 (53 P and 56 D). The sex ratio was, as usual, 2–3 females for every male. All patients were over 16 years of age. There was a wide range of ages, duration of the disease, and degree of severity at the beginning of the trial, similar to what had previously been found in a cross-sectional study of 499 patients at the Committee's clinics.

Two methods of analysis were used: (1) percentages of improvement and deterioration in the two groups from beginning to end of the trial; (2) rates of change per month.

Percentages of improvement in the more objective methods ranged from about 35 to 50 per cent in the different measurements, with very small differences in favor of the drug in some measurements, in favor of the placebo in others. The average (median) rates of change were very small in both groups, e.g., less than one active joint per month. More extreme improvements were 3.6 joints per month in the P group, 2.9 joints in the D group. In some measures these more marked improvements were slightly greater in the D group, in others slightly greater in the P group.

There was no distinction between P and D in the changes from one of the functional classes to another. The physicians' and patients' impressions of over-all change in the disease showed the following scores for improvement: Physicians—37 per cent in P, 36 per cent in D. Patients—48 per cent in P, 51 per cent in D.

The only clearcut difference in the two treatment groups appeared in the week following the withdrawal of the medications at the end of the three-month period. Patients and physicians were still "blindfold"; but both reported their over-all impressions of deterioration greater in patients who had been on the drug than in the placebo patients—about twice the percentage of deteriorations in the D group as compared with the P group. Even though the numbers of patients were small, these differences would occur rather rarely by change alone. The only objective measure that seemed to reflect this difference was a marked increase in the duration of morning stiffness in a few of the D patients, as compared with the P patients.

In all the analyses attempts were made to see whether patients with different duration of disease or severity of symptoms showed differences in response to the drug and placebo; but no such distinctions were found.

General conclusion: In patients of this type, treated and examined as in this trial, with aspirin permitted to all patients, there seemed to be little to choose between indomethacin and placebo.

Undesirable signs and symptoms: On each visit an inquiry was made about the occurrence of 20 different signs and symptoms. For each item the records of patients, in whom that item had not been present at the beginning of the trial, were analyzed to find how many had reported it on one or more of the subsequent visits. The only appreciable differences between the two treatment groups were in headache, dizziness and lightheadedness—about twice as frequent in D as in P (e.g., headache 32 per cent in P, 56 per cent in D).

None of these symptoms were serious, and even in the patients who withdrew before the end of the trial because of disagreeable symptoms, none of the symptoms were at all alarming.

Impact of Advertising and Promotional Activities.—I am not sufficiently acquainted with this topic to discuss it in general, but I have been interested in looking at one part of the evidence on which producers of indomethacin have based rather strong claims for the drug in rheumatoid arthritis of the limbs (peripheral rheumatoid arthritis); namely, the reports of a particular investigator. In a production circular that I received from the Company April 5, 1968, I noted that there was mentioned only one report by that investigator on the use of the drug in peripheral rheumatoid arthritis. It was published in a certain journal in 1964, and it was a half-page abstract of a paper delivered at a meeting of a scientific association. It appears quite impressively in favor of the drug; but papers presented at association meetings often appear impressive. They are interim reports, presented for criticism by the audience, and to establish a claim to a discovery if it should turn out to be a valuable discovery. When a full report of the investigation was published the following year (1965), the evidence was not nearly so impressive. In the most important part, the comparison of placebo and drug-treated patients, there was a serious flaw.

I did not find this full report mentioned in the Company's drug circular, although it contains the note: "Effective December 1967." I am not inclined to blame the drug company for using the evidence from the abstract. It was in the public domain for anyone to quote.

Even if the abstract had been read by experts in a drug-licensing agency, they could not have detected the flaw. I think that they would have been impressed by the evidence and by the reputation of the investigator. Perhaps the only way to stop this kind of thing would be for a licensing agency to refuse to accept abstracts as evidence, perhaps also to frown upon their use in drug publicity.

Safety and Efficacy.—For an over-all judgment on these topics I defer to Dr. O'Brien; but, for what it is worth, I will mention what I would be inclined to do if I were a clinician and had a rheumatoid patent who could not tolerate aspirin. Because of a widespread impression that indomethacin helps some patients, and because of the greater deterioration in some patients in the CCC trial after the drug had been withdrawn, I would be inclined to give indomethacin in preference to other commonly used drugs, and I would watch carefully for adverse effects.

General Comments.—It appears to me that, while the main purpose of this Subcommittee may be the protection of the public in an economic sense, when the Subcommittee is concerned with problems in the field of drug production it is playing a very significant role in the field of health care. This is a very complex area, even regarding the evaluation of drugs alone; and it has occurred to me that perhaps the Subcommittee would find something of interest in a few remarks by one who has been in the field of drug evaluation since the beginning of what can be called "the modern period," that is to say, about the last twenty years.

The "Modern Period" of Drug Evaluation.—This is the period when medical people have come to recognize, more and more, that the only really reliable way to evaluate drugs is by the "controlled trial." The essence of a controlled trial is that one drug is used on one group of patients and, concurrently, there is another group, a control or contrast group, of similar patients, handled in the same way, except that it receives another treatment, either another drug or a placebo. Further, the observations must be made blindfold, or, if that is not possible, they must be made in such a way as to exclude the risk of bias; and there must be systematic observations, the same for both groups.

Although I am not by nature an optimist, when I look back twenty years I am greatly impressed by the progress that has been made in the understanding of the need for controlled trials, not only in the medical profession but among intelligent members of the public. Perhaps members of the Subcommittee, who find so many wrongs to be righted, will also be encouraged by this progress.

"Experiments" on Human Beings.—Controlled trials sound to some people like experiments on human beings, in the sense of using them, not for their benefit, but for one's own ends. Those of us who know what actually goes on in a good drug trial, i.e., a trial conducted by good investigators who are also good doctors, see the matter differently. An important point that many people do not realize is that every time a doctor, in the ordinary course of his work, tries a drug, even a much-used drug, on a patient for the first time, he is performing an experiment. It may do the patient no good, and, with most of the powerful modern drugs, it may do him harm. As a patient, I would much prefer to be in a good experiment, a good drug trial, even taking a 50:50 chance of a placebo, because I would receive more thorough and systematic examinations than can possibly be given to routine patients, and I would know that, if things were going wrong, I would be taken out of the trial.

Pharmaceutical Companies.—The executives of a pharmaceutical company may, as individuals, be altruistic, and their scientists are often of high quality: but we should never forget that the primary aim of a company is commercial. A company can make a quick million or two out of a new drug that is subsequently found to be of no particular value; but some of the more enlightened companies are coming to realize that a succession of such "flash in the pan" drugs does not build a good reputation. We may hope for the spread of such enlightment; but in the meantime we should ask: What can be done to counteract the influence of the market place in drug evaluation?

The most obviously desirable step, it seems to me, would be to take the evaluation of drugs entirely out of the producers' hands. When the Cooperating Clinics Committee conducts a trial it insists that, after the manufacturer has supplied the drug, he and his agents make no further contact with the investigators regarding the trial. Any necessary communication has to be through the coordinator's office. This has not been an easy achievement, because the FDA regulations regarding new drugs confer on the manufacturer the responsibility to produce evidence regarding the value and safety of the drug. The company is the "sponsor" of the trial, and the investigators are to communicate with the sponsor, not directly with FDA. Theoretically, the CCC, or any other group of investigators, could be the sponsor of a trial: and, as coordinator of the CCC studies, I looked into that possibility. I found that we would have to produce for FDA so much evidence regarding the drug (its chemistry, animal experiment results and any previous clinical tests) and go through so many official steps, with the inevitable delays, that I decided to drop the idea of the Committee being its own sponsor.

Even although a pharmaceutical company agrees to avoid contact with investigators during the trial, it can still claim its right, under FDA regulations regarding new drugs, to examine the data, our analyses and our reports, before publication. If a report were adveres to a drug, there is, so far as I can see, nothing to prevent a company introducing such delaying tactics that the investigators would get tired, and the report might not be published at all. In the meantime another report, by other investigators, apparently more favorable to the drug, could have been published.

Support for Drug Evaluation.—Good drug evaluation is expensive. In any large trials there have to be some full-time people in the coordinator's office. Clinical investigators who devote part of their time to a drug trial have to receive some payment. A good part-time secretary is necessary at each clinical center. There are laboratory costs, X-ray costs and so forth.

Much of the money for drug evaluation goes directly from pharmaceutical houses to the clinical investigators. The Cooperating Clinics Committee is very much opposed to this. It accepts the drugs without paying for them, but it will accept nothing else from the drug company, not even a free lunch.

The CCC program is supported entirely by a research grant from the National Institutes of Health, and this is in many ways a desirable form of support, because by this mechanism the investigators must really want to do research and if their proposal is approved by panels of other scientists, outside the Government, it stands a chance of being funded. The Government, in this system, does not produce the money to tempt people who would not otherwise wish to do drug evaluation. (To one who is not interested, the detailed work is boring.) As with all research grants from the Public Health Service, the Government does not *direct* the research.

The chief disadvantage of the PHS research grant mechanism appears to me to be the following. An application for research grant support of a drug evaluation has to take its place, in competition for often limited funds, with applications for many other kinds of medical research, and if a reviewing panel feels that these are more important than drug evaluation, a good proposal may get a low priority and not be funded. It seems that, if the public really feels that good drug evaluation is important, there should be some more assured form of support, and the funds available, whether from public or private sources, should be much larger than they are at present.

The FDA.—During recent years the activities of the FDA have done something to improve the standards of drug evaluation; but this has entailed certain disadvantages. I have reason to believe that in the personnel of the organization there are considerable differences in scientific standing, and understanding. I am not sure that every senior staff member who has to make decisions about drug evaluation really knows what a controlled trial implies.

We may hope that this staffing situation will improve. There is, however, an impediment that is inherent in such a governmental organization—the effect of public opinion. The public is anxious to have more and more powerful drugs, but it is concerned about the disastrous effects of some recent drugs, and does not seem to realize that, to satisfy its desire, risks are inevitable. If something goes wrong with a patient, even in a very careful drug trial, there is a feeling that someone must be to blame; and the natural place to fix the blame is on a government employee who has permitted the trial to take place. It is also natural, therefore, for such employees to try to avoid risks.

In a case with which I was involved recently a very experienced group of investigators proposed to test in rheumatoid arthritis a drug that involved some risks. The drug had been used in another disease for a number of years, and investigators knew how to reduce the risks greatly. All the evidence was supplied to FDA; but the responses from different equally authoritative officials were completely at variance, and it took some six months before an agreed verdict of permission was obtained.

Incidentally, since this drug is available on prescription, it is now being given to rheumatoid patients by some physicians without the precautions that the investigators proposed to take. I feel sorry for FDA officials under public pressure; but it seems that there is room for improvement in the organization.

SUPPLEMENTAL STATEMENT OF DR. DONALD MAINLAND ON "SUBSTANTIAL EVIDENCE"

It seems to me that a very good definition of "substantial evidence" is contained in Section 505 of the Federal Food, Drug and Cosmetic Act, including Drug Amendments of 1962—subsection (d)(6)—beginning as follows: "The term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations . . ." I assume, of course, that "well-controlled" implies the features of a controlled trial that I have outlined earlier in my testimony.

Beyond that, it would be difficult to spell out details, because the risks of biases and the precautions to be taken differ with different drugs and in different trials.

What was thought to be "substantial evidence" in my student days in the early 1920s, or even what was thought substantial by very many physicians in the 1940s, would not be thought substantial by critical investigators today.

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A three-month trial of indomethacin in rheumatoid arthritis, with special reference to analysis and inference

Without questioning the possibility that indomethacin benefits some patients, this 3 month, 11 clinic, blindfold trial studied arthritic symptom changes and the frequency of nonarthritic symptoms in 71 indomethacin-treated (D) and 65 placebo-treated (P) adult patients with peripheral rheumatoid arthritis. Salicylates were permitted to both groups. Five relatively objective measures (numbers of clinically active joints, grip strength, morning stiffness, erythrocyte sedimentation rate, and walking time) were used, and also physicians' and patients' impressions. Corrections were made for initial levels of disease activity. The D and P groups were indistinguishable in frequency, extent and rate of change of symptoms, evaluated either singly or in combination. Undesirable symptoms, especially headache, dizziness, and light-headedness, were more frequent in the D group than in the P group. In the week after trial medication had ceased, and before therapy assignments were revealed, physicians' and patients' impressions reported more deterioration in the D group than in the P group, and this was reflected in the morning stiffness evaluation. Six pitfalls in inferences from such trials are illustrated and discussed.

The Cooperating Clinics Committee of the American Rheumatism Association[*]
New York, N. Y.

In a survey[*] of the literature on indomethacin, extending back to its introduction as an anti-inflammatory drug in 1963, there were discovered 46 reports which specifically dealt with the use of the drug in rheumatoid arthritis. In general the degree of enthusiasm for the drug varied inversely with the quality of the investigation. For example, in those reports that contained no objective measures of joint function, 56 per cent of 607 cases of rheumatoid arthritis were stated to have improved when treated by the drug, whereas in those reports that contained evidence of objective measures only 34 per cent of 218 cases were classified as improved.

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Received for publication Sept. 16, 1966.

[*] The Committee was established in 1958 to develop clinical trial methodology, and has since extended its research to the natural history of rheumatoid arthritis. Accounts of its methods are in references 7 and 9; its published studies are references 2, 10, and 11. Present members: Drs. Charles Ragan (Chairman), William H. Batchelor, John Baum, Roger L. Black, Harvey E. Brown, Jr., Robert Brown, Glenn M. Clark, Alan S. Cohen, John Decker, Gideon K. DeForest, Ivan S. Duff, Ephraim P. Engleman, Louis A. Healey, Ralph A. Jessar, Donald Mainland, John A. Mills, Charles Plotz, Charles L. Short, Irving Steck, Stanley L. Wallace, Howard J. Weinberger, Earl A. Wheaton, Jr., and Nathan J. Zvaifler. Additional representatives of their respective clinics: Drs. James W. Hollingworth, David Kaplan, William M. Mikkelsen, and William M. O'Brien. Consultant: Dr. Louis A. Lasagna. This report was prepared by Dr. D. Mainland, Professor of Medical Statistics and member of the Study Group on Rheumatic Diseases, New York University, and by Miss M. I. Sutcliffe, Biometrician and Coordinator of the Committee's studies. After presentation of a draft to the Committee, the final version was prepared with the assistance of the Publications Subcommittee: Drs. H. E. Brown, L. Healey, D. Kaplan, and W. Mikkelsen.

[*] The survey was made by Dr. M. W. O'Brien in the Yale University Cooperating Clinic. A total of 107 citations were found from the *Quarterly Cumulative Index Medicus, Arthritis and Rheumatism Disease Abstracts*, and *Current Contents*. Twenty of the original reports (3 of them in English) were not obtained for examination.

The reports on rheumatoid arthritis were examined for the presence or absence of the following characteristics:

1. The use of controls, i.e., comparison with another drug (or with placebo) either in another group of patients or in the same patients by a switch-back or cross-over design.
2. Blindfold investigation.
3. Relatively objective methods of assessment, such as the use of a manometer to measure grip strength and of rings to measure joint swelling.

Although many of the authors stated that objective measures had been used, the results and analyses were often based solely on subjective responses. Only one paper,[5] on a comparison of indomethacin with phenylbutazone, satisfied all three criteria. Of the four papers that satisfied the first criterion and one of the other two criteria, one[12] was an indomethacin-phenylbutazone report. The other three, which are more directly pertinent to the Committee's trial, are summarized here:

Wanka, Jones, Wood, and Dixon Study[17]: patient and physician blindfold; sequential switch-back design; indomethacin (200 mg. daily) and placebo on alternate weeks for 6 weeks; 22 patients; 17 expressed preference for indomethacin.

Smyth Study:[15] patient blindfold; alternation of indomethacin (from less than 100 mg. to more than 200 mg. daily), paramethasone, and placebo at arbitrary intervals, determined by apparent stabilization or appearance of maximum benefit, but with transference to the drug when a patient's condition was worsening on placebo; average period 23 weeks; 55 patients (23 lost during the trial); statistically significant differences in favor of indomethacin against placebo in an inflammatory index, shoe-tying time, grip strength, walking time, ring size, and knee circumference, not in five other measures.

Pitkeathly, Banerjee, Harris, and Sharp Study:[13] patient blindfold; switch-back design; indomethacin (50 mg. increased to 100 mg. daily) and soluble aspirin (4 Gm. daily) for alternate 2 week periods; total, 4 weeks; patients on preadmission corticosteroids were maintained on the same dose throughout the trial; 42 hospital inpatients (38 completed the study); spontaneous improvement, regardless of the drug, was attributed to hospitalization; increase of grip strength was somewhat greater on indomethacin (statistically significant at 5 per cent level); decreased swelling of proximal interphalangeal joints, measured by ring size, was very similar during treatment with both drugs; 21 patients expressed preference for aspirin, 13 for indomethacin.

In the first two of these three studies, aspirin intake was apparently not controlled or investigated.

Regarding untoward symptoms in patients receiving indomethacin, these reports and the total survey of the literature gave the impression that the frequency of such symptoms has not appreciably diminished since capsules were substituted for tablets as the means of administration.

Objectives of the trial

In spite of the poor quality of much of the previous research on indomethacin, there seemed to be no reason to doubt that the drug had some beneficial effects on some patients. Therefore, the Committee did not enter the trial for the purpose of testing the hypothesis that there was no difference whatever between the therapeutic effects of the drug and the changes observed during placebo treatment. It wished, rather, to ascertain (1) the magnitude of placebo-drug differences in outcome, and (2) the placebo-drug contrast in the frequency and degree of undesirable symptoms. For three reasons the Committee decided not to attempt to deprive the patients of salicylates:

1. In routine therapy, where the results of a trial should be applicable, salicylates are commonly permitted in conjunction with other antirheumatism therapy.

2. The forbidding of aspirin would probably increase the loss of dissatisfied patients.

3. If aspirin were forbidden there would probably be unrevealed consumption of it, and the knowledge of this possibility would increase the difficulty of interpreting the results.

The study was, therefore, a comparison of indomethacin with placebo, salicylates being permitted with both treatments.

Criteria of admission to the trial

The patients were to be outpatients (or domiciliary hospital patients) of either sex, any ethnic group, and any occupation, with "classical" or "definite" peripheral rheumatoid arthritis (American Rheumatism Association criteria[14]) which had become manifest after the sixteenth birthday. In addition to the 20 exclusions in the American Rheumatism Association criteria (e.g., high concentration of lupus erythematosus cells, scleroderma, infectious arthritis, Reiter's syndrome, and gouty arthritis), the following conditions excluded patients: presence of the arthritis for less than 6 months, pregnancy or childbirth, severe infection, major surgery within the previous 6 months, anemia other than the anemia associated with rheumatoid arthritis, cancer, diabetes, serious kidney disease, serious liver disease, known or suspected peptic ulcer, psoriasis, severe hypertension, active tuberculosis, ulcerative colitis, and known or suspected ankylosing spondylitis (but the screening of patients by sacroiliac radiography was not obligatory).

Antirheumatism therapy exclusions were: (1) indomethacin at any time previously; (2) systemic or intra-articular corticosteroid, phenylbutazone, or any antimalarial drug, during the previous 2 months; and (3) gold therapy if the patient had received less than 1 Gm. in the 6 months preceding the last injection or any gold within the 2 months prior to the trial.

It was recommended that patients be excluded if there was doubt of their dependability with regard to attendance at scheduled times or their likelihood of completing the trial.

Therapy

Indomethacin (Indocin) was administered in capsules, each capsule containing 25 mg. The placebo contained in each capsule 223 mg. lactose and 2 mg. magnesium stearate.

The scheduled daily numbers of capsules of drug or placebo and the milligrams of drug per day were as follows: weeks 1 and 2, 2 capsules (50 mg.); weeks 3 and 4, 4 capsules (100 mg.); weeks 5 through 8, 6 capsules (150 mg.); weeks 9 through 12, 8 capsules (200 mg.). Capsules were to be taken after meals and spread through the day. Physician observers were free to reduce the dosage if undesirable symptoms occurred, but they were urged to keep the reduction minimal.

Assignment of drug or placebo was performed by random numbers at the Coordinating and Biometrical Center, and the bottle labels bore only the clinic name and the patient's serial number (1, 2, etc., in order of admission to the trial).

One of the coordinators (M. I. Sutcliffe) and an assistant inspected the drug supplies at the manufacturer's distributing center immediately before shipment to the clinics. At each clinic the drugs were received by a specially designated drug recipient, a responsible person who had no other connection with the trial, and who removed from each bottle and sent to the Coordinating Center the detachable label, which, in accordance with United States Post office regulations, bore the identification (drug or placebo).

There was no occasion to refer to the assignment list while patients were still in the trial, and the biometricians who were to analyze the data kept themselves in ignorance until all the data were collected and decisions regarding problem cases (e.g., withdrawals from the trial) had been made.

During the trial and for one week after the trial medication had ceased, the patients were not to receive systemic or intra-articular corticosteroids, antimalarials, phenylbutazone (Butazolidin), gold, or nontrial indomethacin. Consumption of salicylates was to be in accordance with individual clinic practice. Reports on all types of therapy were required at each visit; patients were instructed to return their trial therapy bottles, so that unconsumed capsules could be counted.

Methods of assessment

The methods of assessment, described in more detail in the Committee's report on its 7 day variability study[2] and elsewhere,[9] were as follows:

1. Number of clinically active joints—determined by any one of the following: tenderness on pressure, pain on passive movement, or swelling other than bony proliferation. The scheme contains a total of 66 joints (or groups of joints, e.g., the wrist) including the temporomandibular but excluding the hip, because swelling of that joint is indeterminable. Recorded also were heat, ankylosis (determined by clinical examination), and subcutaneous nodules. Radiographic assessment in a trial of this duration was not considered worth while, and, therefore, the American Rheumatism Association classification by stages of progression[16] was not applied.

2. Grip strength—determined by a folded pressure cuff attached to a mercury sphygmomanometer, with the patient's arm unsupported. Initial inflation was to 20 mm. Hg. Height of the column was to be read when maintained by squeezing (not at initial spurt); an average of 3 right and 3 left readings was taken.

3. Duration of morning stiffness—to be estimated for the previous day and for an "average" day during the previous week.

4. Walking time—the time required to walk a straight continuous distance of 50 feet as fast as possible (without running) from a standing start.

5. Erythrocyte sedimentation rate (ESR)—determined by the Westergren method; 3.8 per cent sodium citrate as anticoagulant; one hour reading taken.

6. Patient's assessment—his impression regarding his arthritis as good, fair, or poor, and as worse, about the same, or better as compared with his condition on the previous visit.

7. Observer's over-all assessment—recorded in the same terms as the patient's assessment, taking into account not only the impressions gained by the measurement methods, but also any other available information.

8. American Rheumatism Association functional classification[16] with reference to the patient's usual occupation.

Rheumatoid factor tests—sheep cell agglutination and latex tube tests, performed at a central laboratory (the Dallas clinic).

Routine blood tests—white blood count, blood urea nitrogen, serum glutamic oxaloacetic transaminase, and alkaline phosphatase. Methods (p. 30) were selected by the individual clinics. Urine was also examined for albumin.

Visits were scheduled at 4 week intervals, beginning with visit 1 (V1) when the trial therapy was started. The therapy was stopped on visit (V4), and the patients were re-examined one week later (V5). In addition there was an unnumbered interim visit, 2 weeks after V1, when the first increase of dosage was made.

All the foregoing 8 numbered observations and all the routine blood and urine tests were made on each of the 5 numbered visits. On each of these visits, and also on the interim visit, inquiries regarding undesirable signs and symptoms were made according to a list of twenty items (p. 29). Blood for the rheumatoid-factor tests was collected on V1 and V4.

Most of the observations were made within ± 3 days of the scheduled dates. Causes of departures from these dates were reported, so that allowance could be made for them in analysis of the data.

The duration of the trial was approximately 10 months. The first patient was admitted on November 11, 1964. The last patient completed the trial on September 8, 1965.

Observers

The trial was conducted at 11 of the clinics, which were very familiar with the techniques and recording methods. The names of the observers, of the rank of clinical fellow or higher, are given on p. 36. With very rare exceptions, all examinations on any particular patient were made by the same observer.

Analysis of data

Classification of disease activity. The activity of the disease in the four chief measures (number of clinically active joints, grip strength, duration of morning stiffness, and erythrocyte sedimentation rate) was classified by the tables developed from the 499 patients in the Committee's 7 day variability study[2] of patients on all types of therapy. In that study, the patients had been arranged, from the day 1 records, in order, from the least active to the most active for each measure separately, and had then been grouped in 10 classes (A through J) containing as nearly equal numbers (10 per cent) as possible.

After the first examination, 411 of the variability study patients had been maintained on the same therapy and the same dosage (except for some fluctuation in salicylate consumption) for one week and had been examined on day 8 by the same observers as on day 1. From these patients' data, tables were constructed to show the classes to which they had moved.

In the indomethacin trial the data from the variability study were used for three purposes: (1) to ascertain whether the patients at the beginning of the trial displayed a range of variation similar to that observed in the variability study; (2) to compare changes in drug and placebo patients within each of the day 1 classes A through J (This matching increases the sensitivity of a trial because, as was illustrated by the variability study, the amount of variation in level of a measure of activity depends partly on its initial level. It may show also that a drug which does not appear very effective in the total group of patients is more clearly effective in more active, or less active, cases.); (3) to compare the amount of change during the 3 months of the trial with the amount of change exhibited by the variability study patients in one week. This was done by correcting for the differences in initial severity between the trial patients and the variability study patients.

For example, in the variability study, of the patients who were in the articular severity class C (6 to 8 clinically active joints) on the first day, 45.2 per cent of them were in the same class one week later, 7.1 per cent had improved (were in class B, 4 to 5 active joints), and 47.6 per cent had deteriorated (were in class D, 9 to 11 active joints, or lower). In the indomethacin trial, 7 of the drug-treated patients were in class C on visit 1. If in the three months of the trial they had behaved, proportionately, as did the variability study patients in one week, on the fourth visit 45.2 per cent of them (3.16) would have been in class C, 7.1 per cent (0.50) would have improved, and 47.6 per cent (3.33) would have deteriorated. These estimates can be called the "variability study expected values." The actual numbers in the 7 drug-treated patients were 3 in class C, 3 had improved, and 1 had deteriorated.

By adding together the various "expected" numbers from all classes (A through J) there were found the total numbers (unchanged, improved, deteriorated) that would have been found if in each severity class the trial patients had shown the same proportional amount of change as did the variability study patients; the numbers were then expressed as percentages of the total number of patients. (The term "unchanged," of course, does not imply that these patients had not moved temporarily into other classes during the trial.)

Average rates of change. In order to

measure more precisely the changes that occurred during the trial and to compensate in part for observational variation, an average rate of change per month was estimated from the four readings (e.g., numbers of clinically active joints on V1, V2, V3, and V4) in each patient. For convenience, the method of least-squares straight-line fitting was used, without any implication that the change was strictly linear (any more than one assumes a linear change in finding the difference between a single pair of readings, initial and terminal). For simplicity, these average rates of change will be referred to as "gradients."

There was no implication of, or attempt to test, the "significance," statistical or clinical, of the individual gradients. The purpose was to compare the placebo- and drug-treated groups with respect to the directions and magnitudes of the gradients.

Random frequency tests. Because the objective was not to test a null (no difference) hypothesis, random frequency tests (misleadingly called "significance" tests) played a much less prominent part in the analysis than is usual in clinical trials. A placebo-drug difference in a certain observational criterion might be "highly significant," i.e., would very rarely be produced by the random assignment alone, but it might not be large enough to interest a therapist. On the other hand, a difference might be far from "significant," i.e., such differences would often be produced by the randomization alone, but this would not prove that some patients had not benefited from the drug.

Random frequency tests are of greater use in an earlier phase of drug testing, when they help one to decide whether it appears worthwhile to develop a product for much more extensive study. In this trial they were employed mainly for three reasons:

1. It was of interest to see whether a particular placebo-drug difference would be produced frequently or rarely by the randomization alone.
2. If two different measures of effect (either therapeutic or toxic) differed greatly in their placebo-drug difference, as evaluated by a random frequency test, this would suggest a clue to the mode of action of the drug or to a difference in sensitivity of the two measures.
3. When incidental observations were made (such as the greater frequency of more active disease in the indomethacin-trial patients than in the variability-study patients), it was desirable to have a device for distinguishing between differences that would often occur by chance and those that would justify speculation regarding other causes (and possibly further investigation).

The tests used were chiefly chi-square (with Yates' correction) for fourfold tables of frequency data and the Wilcoxon-White two-sample ranks test[8] for the comparison of means. The random frequency (probability) is symbolized by "Pr" instead of the more usual "P," which is employed here as the symbol for placebo.

Numbers and characteristics of patients

The number of patients qualified by protocol and entered in the trial was 141. Five were disqualified shortly after the beginning of the trial for the following reasons: uveitis, asthma, bronchitis, alcoholism, and departure from the city; they are excluded from this report. Of the remaining 136 patients, 65 were on placebo (P) and 71 on the drug (D). There were 38 men and 98 women. Numbers of patients per clinic were 1, 5, 6, 8, 10, 14 (2 clinics), 18, and 20 (3 clinics).

Ages of patients: median, between 52 and 53 years; extremes, 16 and 81 years (one patient each); 10.3 per cent, 16 to 35 years; 9.6 per cent, 59 to 81 years.

Duration of disease: median, between 5 and 6 years; extremes, 6 months (6 patients) and 36 years (2 patients); 8.1 per cent, 6 to 11 months; 10.3 per cent, 25 to 36 years.

The two treatment groups did not differ appreciably in the distributions of age or disease duration.

Degree of disease activity. The patients were widely distributed among the ten

Table I. *Clinical activity on visit 1 of indomethacin trial classified as in 7 day variability study (VS)[2]; total number of patients was 136*

	No. joints		*Grip strength (mm. Hg)*			*ESR (mm. in 1 hour)*		*Morning stiffness*	
			Range						
Class	*Range*	*No. patients*	*Males*	*Females*	*No. patients*	*Range*	*No. patients**	*Range*	*No. patients†*
Extreme classes									
A	0-3	9	253.9 and over	187.1 and over	7	1-11	6	0 minute	12
J	37-66	14	55.5 and under	48.6 and under	12	92-158	9	5 hours to all day	16
Less severe (50% in VS)									
A-E	0-14	48 (35%)	123.9 and over	97.6 and over	53 (39%)	1-41	58 (50+%)	0-1.25 hours	57 (42%)
More severe (50% in VS)									
F-J	15-66	88 (65%)	123.8 and under	97.5 and under	83 (61%)	42-158	57 (50−%)	1.5 hours to all day	77 (58%)

*All data from one clinic were excluded because it reported that its laboratory work was unreliable.

†Two patients were excluded because morning stiffness on visit 1 was reported "indefinite."

variability study classes, i.e., in these four measures of activity they could be considered fairly representative of the patients commonly found in these clinics. However, Table I shows that in all four measures the ratio of more active (in classes F through J) to less active (A through E) was greater in the trial patients than in the variability study. In morning stiffness and ESR the differences could well be due to chance, but this was not so likely in grip strength (Pr from chi-square test, between 0.05 and 0.02) or in joint numbers (Pr less than 0.01). The two treatment groups were similar in this characteristic. Such differences from the variability study were not surprising because that survey contained most of the available patients at some of the clinics, including patients who took no antirheumatism drugs except an occasional aspirin tablet, and would not be considered suitable for the trial of a drug such as indomethacin.

American Rheumatism Association functional classes. The distribution of the 136 patients was similar to that of 498 variability study patients (Table II).

Table II. *Distribution of patients in functional classes*

	Trial		*Variability study*
Class	*No.*	*%*	*%*
I	14	10.3	8.6
II	75	55.1	52.4
III	44	32.4	35.3
IV	3	2.2	3.6

Selection effects of drug exclusion. In all trials of a drug that has been in use for several years, especially in chronic diseases, the exclusion of patients who have previously received the drug can greatly reduce the number of available patients, e.g., in the indomethacin trial only one patient was entered by a clinic which had provided many patients for the Committee's previous studies. In itself this would not produce bias, but there are also other ill-defined restrictions on the type of patients in the trial. Even if the cases are not predominantly mild or early, they may be cases that have, until just before the trial, been so mild as to have received only aspirin, and then have suddenly developed greater severity that qualified them, in their physicians' opinion, for admission to the trial.

Moreover, some patients may have qualified for the trial because their physicians, not believing in the drug, had administered various other therapies; their therapeutic histories will differ somewhat from the histories of patients who, in the hands of other physicians, have been rendered ineligible because they have previously received the drug.

In this trial the analysts could see no way of detecting such factors, which constitute one of the reasons why such a trial, however large and well conducted, cannot be assumed to give the final precise verdict on a drug.

Withdrawals during the trial

Of the 136 patients (65 P, 71 D), 27 withdrew (12 P, 15 D) at various times during the trial. As usual, it was impossible to distinguish clearly, as reasons for withdrawal, between unpleasant (nonarthritic) symptoms thought to be attributable to the drug and a patient's belief that he was failing to benefit from the treatment. As far as could be determined the predominant reasons were as shown in Table III.

The initial classifications of disease activity of the 27 patients who withdrew were compared with the classifications of the total 136 patients. For joint numbers and morning stiffness the figures were as given in Table IV.

There was a suggestion that patients with more severe symptoms had a greater tendency to withdraw than patients with milder symptoms (Pr from chi-square for joints was 0.05 to 0.02, for morning stiffness was 0.2 to 0.1), but this was not confirmed by the figures for grip strength, ESR, or functional class.

Selection due to withdrawal during the trial. The 109 patients (53 P, 56 D) who remained in the trial to the end were to some extent selected by indefinable criteria, owing to the mixture of factors (nonarthritic symptoms, lack of apparent benefit, and unrevealed determinants) that induced the 27 patients to withdraw. The results from the 109 patients may, therefore, contain certain hidden biases in favor of or against the drug. For therapeutic prediction the results merely indicate what could be expected to occur in patients, similar to those in the trial, who did not entirely cease taking the drug within 3 months for the complex reasons that prompted the 27 patients to withdraw.

Table III. *Reasons for withdrawal from the study*

	Placebo		*Drug*	
Reasons	*No.*	*% of 65*	*No.*	*% of 71*
Undesirable symptoms	7	10.8	10	14.1
Worsening of arthritis	2	3.1	5	7.0
Disappearance of patient	3	4.6	–	–
Total withdrawals	12	18.5	15	21.1

Table IV. *Classifications of disease activity in patients who withdrew from the study*

		No. at visit	*Withdrawals*	
Measure	*Class*	*1*	*No.*	*%*
No. clinically active joints	A-E	48	4	8.3
	F-J	88	23	26.1
Morning stiffness	A-E	57	8	14.0
	F-J	77	19	24.7

Frequency of changes in four measures of activity

Method of expression. In Table V the changes in disease activity are expressed in terms of the ten severity classes in the variability study tables.[2] Those tables enable one to take account of the magnitude of a change in addition to its direction, and they do so without the necessity of reporting absolute values (e.g., millimeters of grip

Table V. *Changes in four measures from visit 1 to visit 4, classified as in the 7 day variability study (VS)*[2]

Measure	No. patients	Deterioration				No change†		Improvement			
		Extreme*		Total				Total		Extreme*	
		No.	%	No.	%	No.	%	No.	%	No.	%
No. clinically active joints											
Placebo	53	4	7.5	13	24.5	14	26.4	26	49.1	7	13.2
Drug	56	6	10.7	12	21.4	15	26.8	29	51.8	7	12.5
P + D	109	10	9.2	25	22.9	29	26.6	55	50.5	14	12.9
Expected VS (%)‡			4.0		28.8		33.2		38.0		7.1
Grip strength											
Placebo	53	5	9.4	15	28.3	16	30.2	22	41.5	5	9.4
Drug	56	6	10.7	21	37.5	15	26.8	20	35.7	7	12.5
P + D	109	11	10.1	36	33.0	31	28.4	42	38.5	12	11.0
Expected VS (%)			2.4		23.9		47.5		28.6		3.6
Morning stiffness											
Placebo	51	5	9.8	15	29.4	16	31.4	20	39.2	11	21.6
Drug	56	3	5.4	15	26.8	12	21.4	29	51.8	12	21.4
P + D	107	8	7.5	30	28.0	28	26.2	49	45.8	23	21.1
Expected VS (%)			6.4		23.5		51.9		24.6		4.1
Erythrocyte sedimentation rate											
Placebo	47	11	23.4	17	36.2	14	29.8	16	34.0	3	6.4
Drug	48	8	16.7	23	47.9	8	16.7	17	35.4	8	16.7
P + D	95	19	20.0	40	42.1	22	23.2	33	34.7	11	11.6
Expected VS (%)			4.9		28.2		41.3		30.5		4.5

†No change indicates that a patient was in the same VS class on visit 4 as on visit 1.

*Extreme deterioration or improvement indicates changes that occurred in fewer than 10 per cent of the VS patients.

‡Expected VS (%) indicates the percentages that would have been found if the trial patients had shown proportionately the same amount of change as the VS population.

Excluded patients: Under heading of morning stiffness, two were excluded whose stiffness on visit 1 was reported "indefinite." Under heading of erythrocyte sedimentation rate, all 13 patients from one clinic, which reported that its laboratory work was unreliable, were excluded. One other patient was excluded because data were missing.

strength) which would have to be specified separately for each initial level.

For example, of the variability-study patients who started in articular class C (6 to 8 clinically active joints), fewer than 10 per cent had moved to class F (15 to 19 active joints) or beyond by day 8. Of those who started in class D (9 to 11 active joints), fewer than 10 per cent had moved to class G (20 to 24 active joints) or beyond by day 8. The tables provide such 10 per cent cut-off points for deterioration and for improvement in the various initial classes; in the indomethacin data all patients who had by the end of the trial moved beyond these points were classified as having shown "extreme" deterioration or improvement, to indicate a degree of change that was relatively rare in the 7 day study, where the changes in the vast majority of patients could be attributed to inconsequential fluctuations and observational variation.

This method provides not only a simple means of classifying degree of change in an individual group of patients, but also increases the possibility of detecting in a drug trial a difference (large benefit to a few patients) which might be obscured by attention merely to plus and minus signs or to mean values.

Results. Throughout Table V the percentage frequencies in the placebo- and drug-treated groups are very similar. Even the relatively large P-D difference in the frequency of improvement in morning stiffness (12.6 percentage points) would occur in about 30 per cent of randomization experiments. This lack of "statistically significant" differences is, however, not the important point. Even if a trial, conducted on many more patients, proved that the differences, apparently in favor of the drug, were very probably caused by the drug, the figures presented here do not suggest that the differences would have much therapeutic significance.

When the P-D comparisons were made for each measure within each of the ten classes (a matched comparison), there was found no suggestion of a consistent P-D difference and no suggestion that benefit from the drug depended on the degree of clinical activity.

Since there was no appreciable difference between the P and D groups, they were pooled for comparison with the changes shown by the variability study patients in 7 days. The "expected" variability-study percentage (p. 15) represented what would have been found if the variability-study patients had started with the same relative frequencies in the severity classes as did the trial patients, but had then shown the same degrees of change as they actually did in one week. When these estimates are compared with the observed percentages in the trial patients, two features are notable:

1. The patients in the 3 month trial show a greater frequency of change (more than 70 per cent) than would be expected from the one-week variability study (50 to 65 per cent), and also a greater frequency of "extreme" change.

2. Among the patients who changed classes, the variability-study estimates show in all four measures somewhat more frequent improvement than deterioration. This was true of the actual trial patients, chiefly in the active joint numbers and morning stiffness, but not in ESR.

Gradients of five measures during the trial

Table VI shows that the average (median or mean) gradients, i.e., rates of change per 28 day month, were very slight in both treatment groups, and even if, assuming that the slopes were straight throughout the trial, one multiplied each average by 3 to estimate the average total changes in the 3 months of the trial, these also would be very small.

The lower and upper 10 per cent points, enclosing between them approximately 80 per cent of the individual patients' gradients, give a more reliable estimate of variation than do the extreme values which in some instances represent single outlying individuals.

Both in the average gradients and interpatient variation in gradients, the placebo and drug groups are very similar. The differences might well be due to the random assignment of treatments, and they are not consistently in favor of either treatment.

Although the average gradients are not "significantly" different from zero, the last column of the table shows that in 7 of the 10 subgroups there was a slightly higher proportion of upward slopes (indicating improvement) than of downward slopes. This is the same phenomenon as is found in Table V by comparing the percentage frequencies of improved and deteriorated patients. The upper and lower 10 per cent points in Table VI show a similar phenomenon, because in most instances the positive (improvement) value is greater than the corresponding negative (deterioration) value.

This seems to quantify a phenomenon which is well known in general terms, although sometimes forgotten in drug trials that lack controls. In a disease that fluctuates in activity, therapy is often started, or changed, when the disease is in a more active phase. Therefore, within a certain

Table VI. *Gradients (average monthly rates of change) in five measures of disease activity, from readings on visits 1, 2, 3, and 4 (a minus sign indicates deterioration, a plus sign improvement)*

Measure	*No. patients*	*Maximum deterioration*	*Lower 10% point*	*Median*	*Mean*	*Upper 10% point*	*Maximum improvement*	*Patients improved*	
								No.	*%*
No. clinically active joints									
Placebo	53	10.5 –	2.4 –	0.7 +	0.49–	3.6 +	7.6 +	30	57
Drug	56	6.0 –	3.1 –	0.3 +	0.16	2.9 +	6.6 +	33	59
Grip strength (mm. Hg)									
Placebo	53	9.2 –	4.4 –	0.7 +	0.87+	6.0 +	10.5 +	30	57
Drug	56	24.1 –	4.9 –	0.1 –	0.22–	5.8 +	11.3 +	27	48
Morning stiffness (hours)									
Placebo	51	4.66–	0.42–	0.02+	0.06+	1.04+	1.70+	26	51
Drug	56	1.16–	0.37–	0.05+	0.22+	1.07+	2.24+	32	57
50 foot walk (minutes)									
Placebo	44	3.10–	1.25–	0.15+	0.28+	2.40+	3.30+	26	59
Drug	52	8.80–	0.90–	0.20+	0.57+	2.47+	12.50+	31	60
Erythrocyte sedimentation rate (mm. in 1 hour)									
Placebo	45	13.8 –	9.6 –	0.8 –	1.08–	5.7 +	22.5 +	20	44
Drug	46	18.7 –	10.3 –	0.0	0.72+	14.9 +	25.3 +	21	46

Exclusions: In morning stiffness, 2 patients (P) whose duration of stiffness was "indefinite" on visit 1 were excluded. In 50 foot walk, 9 P and 4 D were excluded who used walking aids. In ESR, all 13 patients from a clinic that reported doubt regarding reliability of laboratory data were excluded, and 5 others from whom some data were missing were also excluded.

In grip strength, the maximum deterioration (24.1–) was in a patient whose sole signs of hand involvement were increasing stiffness of the right hand and marked reduction of grip in both hands. (All other patients had definite hand involvement.) Zero gradient was found in one patient (P) who had maximum recordable readings (260 mm. Hg) throughout the trial. In morning stiffness, zero gradients were found in 4 P and 3 D; of these, 2 P and 2 D reported no stiffness throughout the trial. In the 50 foot walk were included two patients who were reported on all visits as having no clinically active lower limb joints; in one of them (P), the gradient was 0.26+, in the other (D) it was 0.05+.

period thereafter, there will be a somewhat higher frequency and degree of improvement than of deterioration. In addition, there is, of course, the "placebo effect" or "Hawthorne effect"[8] of the study itself.

Relationship of P-D differences to patients' characteristics

In the foregoing analyses the sexes were pooled, and there was in both treatment groups a great diversity of age, duration of disease, and titer of rheumatoid factor. Therefore, it was desirable to ask whether a drug benefit had not thereby been masked. If so, it might be possible in routine therapy to select subgroups that appeared most likely to benefit from the drug.

Sex, age, and disease duration. In the five measures shown in Table VI the P-D comparison of gradients was now made separately in the two sexes, in two age classes (up to 50 and over 50 years), and in two duration classes (up to 5 and over 5 years). In all the comparisons the P-D differences in frequency of positive and negative gradients could easily have been fortuitous, and there was among the five measures no consistent suggestion in favor of or against the drug.

There was clearly no point in applying

a more sensitive test, comparison of mean gradients within the subgroups, in order to discover perhaps an occasional "significant" difference. However, in order to see whether correction for differences in age or disease duration might make a more distinct P-D difference, the correlations between these two variables and the joint-number gradients were estimated in the 56 drug-treated patients. Spearman's rank-order coefficient is adequate for such an exploration, and its values were: for age, -0.121 and for disease duration, -0.00075. The effects of correction by these variables would obviously have been trivial.

Rheumatoid factor. The sensitized sheep cell agglutination titers obtained on visit 1 for 81 patients (36 P and 45 D) were available for analysis. There was no distinction in titer frequencies between the P and D groups. The titers were as follows: negative titers (1:14 or below): 28 (35 per cent); median, between 1:56 and 1:112; upper 8.6 per cent, 6 patients at 1:896 and 1 patient at 1:3584.

In none of the five measures in Table VI did the gradients (classified as positive or negative) show any appreciable distinction in P-D differences between patients with positive and those with negative titers. In the drug-treated patients with positive titers, Spearman's rank-order coefficients of correlation of titer with gradient of activity were: active joint numbers (27 patients), +0.227 (Pr, slightly less than 0.3) and ESR (21 patients), +0.025 (Pr, very large).

There was, therefore, no suggestion that the rheumatoid factor test would assist in the prediction of response to the drug.

Over-all assessments

The physician observers' assessment on V3 and V4 (worse, about the same, or better than one month ago) were obtained on 91 patients who had been examined by the same observer on both visits and had not been more than 3 days late for either visit (to avoid effects of insufficient therapy). The possible scores were: 2–, 1–, 0, 1+, 2+. The same patients' own impressions were scored in the same way. The results, with percentage frequencies, are presented in Table **VII**.

In both treatment groups the physicians' scores were zero (no persistent change in either direction) in about half the patients, negative in about one sixth, and positive in about one third. As in the Committee's previous studies, patients registered a change more frequently than did the physicians. Both groups reported improvement more frequently than they reported deterioration, but they did not differ greatly from each other in the ratio of these two types of change.

American Rheumatism Association functional classes

The variability study[2] showed that this scheme of classification is of questionable validity because of the frequency with which the same patients were classified by the same observer differently on day 1 and day 8; but if in a double-blind trial a striking difference between two treatment groups were observed, it ought not to be ignored. Within each of the four functional classes as reported on V1 in this trial, the P and D patients were compared with respect to their classification on V4. The differences were trivial and not consistently in favor of either drug or placebo.

The P and D patients were then pooled for comparison with the changes reported in the 7 day variability study. Of 72 patients who were in classes I or II (less incapacitated) at the beginning, 6 (8.3 per cent) changed to class III—a negligible difference from 3.7 per cent of 241 variability-study patients. Of 37 patients in classes III or IV (more incapacitated) at the beginning, 14 (37.8 per cent) changed to classes I or II—a great difference from 4.7 per cent of 169 variability-study patients (Pr from chi-square very small).

Adjustments for fluctuating changes

Although initial values of a measure such as grip strength can be used to increase the sensitivity of a comparison of two

Table VII. *Physicians' and patients' assessments of change on V3 and V4*

		Possible scores					
		2− or 1−		*0*		*1+ or 2+*	
	No. patients	*No.*	*%*	*No.*	*%*	*No.*	*%*
Physicians							
P	46	6	13.0	23	50.0	17	37.0
D	45	10	22.2	19	42.2	16	35.6
Patients							
P	46	12	26.1	12	26.1	22	47.8
D	45	14	31.1	8	17.8	23	51.1

Table VIII. *Comparison of changes in clinical activity in two periods, V1 to V2 and V2 to V4 (a minus sign after a mean indicates deterioration, a plus sign improvement)*

Measure	*No. patients*	*Mean change V1 to V2*	*Mean change V2 to V4*	*Correlation between V1 to V2 and V2 to V4*	*Adjusted mean change V2 to V4*[*]
No. clinically active joints					
Placebo	53	1.85+	0.13+	−0.19	0.40+
Drug	56	0.27+	0.25+	−0.36	0.33+
Grip strength (mm. Hg)					
Placebo	52	0.63+	1.77−	−0.33	1.57−
Drug	55	10.45+	7.26−	−0.48	4.64+
Morning stiffness (hours)					
Placebo	46	0.05−	0.35+	−0.35	0.34+
Drug	53	0.73+	0.13+	−0.34	0.36+
Erythrocyte sedimentation rate (mm. in 1 hour)					
Placebo	45	0.27+	1.91−	−0.24	1.85−
Drug	46	5.33+	1.89−	−0.30	0.73−

[*] Adjusted mean changes V2 to V4 were estimated by linear regression for zero change in V1 to V2.

Exclusions: Under heading of grip strength, 1 P and 1 D were excluded because they reached the maximum recordable level at V1. Under morning stiffness, 2 P with "indefinite" duration at V1 were excluded; 5 P and 3 D that reported no morning stiffness at V1 were also omitted. Under ESR, the same patients were excluded as noted in the footnote to Table V.

drugs, a still more sensitive comparison can be obtained by using the change of level that each patient shows under stable conditions in a pretrial period. Such data were not available in this trial, but the data from the first month (V1 to V2) were used in studying the changes in the succeeding 2 months (V2 to V4).

Table VIII shows the mean changes in these periods. The only noteworthy P-D differences are in the first period—grip strength and morning stiffness. The grip-strength difference is the only one in either period that suggested the possibility of something more than a randomization effect (Pr from a two-sample ranks test was approximately 0.06). In the second period, however, this P-D difference was reversed. In the P group a small positive value was replaced by a small negative value, but in the D group a relatively large positive value was replaced by a relatively large negative value. Similar relationships are seen in other parts of the table, but they are demonstrated more clearly by the correlation coefficients, which show the relationships between the V2 to V4 changes and the V1 to V2 changes in the same patients. All the coefficients are negative. That is, the greater the change in one direction (e.g., improvement) in the first month, the smaller, on the average, was the change in that direction (or the greater was the change in the opposite direction) during the next 2 months.

This relationship could be partly due to observational variation. For example, if V1 and V4 readings were accurate, but the V2 reading was erroneously low, a downward movement in the first period would be accompanied by an upward movement in the second period. In the main, however, the coefficients probably represent real fluctuations of symptoms. The actual causes are immaterial in an attempt to correct the V2 to V4 differences. It is immaterial, also, whether the coefficients are "statistically significant" or not (although the five largest have Pr values less than 0.05).

Although it need not be supposed that the relationships were strictly rectilinear, straight-line regression equations with the V1 to V2 changes as the independent variables were sufficient for the exploration. By making $V1 - V2 = 0$ in each equation, the "adjusted" mean V2 to V4 changes in the last column of Table VIII were estimated, and the P and D values in the second period could thus be compared after allowance for their differences in the first period. In active joint numbers and morning stiffness the adjustment reduced the observed V2 to V4 difference between the treatment groups; in grip strength and ESR there was a trivial increase.

The relationships between the changes in two successive periods can introduce serious error in a trial in which the transference of a patient from one drug to another is determined by his current symptoms. For example, if patients whose conditions are thought to be deteriorating on a placebo are transferred to a drug[15] the fluctuation of symptoms can create a spurious verdict in favor of the drug. In a true switch-back trial the periods on each therapy are predetermined.

Combination of measures

In an early phase of drug testing, when none of the individual measures of effect has shown convincing evidence of a difference between two agents, it is often desirable to find out whether a combination of the measures will provide sufficient evidence to justify further development of a drug. In a later phase, such as the present trial, which aims at providing information for guidance in routine therapy, such a composite index is confusing and may be misleading.[9] However, it was of interest to see whether a simple method, which had been successful in an antimalarial trial,[11] would provide better discrimination between the placebo and drug-treated patients than did the individual measures.

A simple method. In this test, walking time was not utilized because patients who had used walking aids had been excluded from Table VI, and all the patients at the clinic that had reported unreliability of ESR data were also excluded. On each of the four measures (joint numbers, grip strength, morning stiffness, and ESR) the actual difference (not simply the class difference) between the V1 and V4 readings was recorded as positive if it was in the direction of improvement, negative if in the reverse direction. A patient might, therefore, have any score between 4– and 4+.

The test failed completely to discriminate between the two treatment groups. For example, when patients with zero scores (8 out of 45 P, 14 out of 48 D) were eliminated, the groups contained almost identical proportions of patients with positive scores (24 out of 37 P, 22 out of 34 D). When ESR was eliminated and the same kind of scoring system was applied to the three clinical measures alone, very similar results were obtained—positive scores in 31 out of 49 P and in 35 out of 53 D.

A more efficient method. When a combination of measures is justified, if a simple method is ineffective it is desirable to give the observations a maximum opportunity to demonstrate a difference between the therapies under test. For this it is necessary to use the actual observations instead of a scoring system and to seek the most effective weight for each measure, instead of using equal weights or weights determined by an impression of relative importance, or even by noting which measures had given the lowest probability values in the individual comparisons of the therapies.

A method that meets the requirements is the "discriminant function" technique invented by Fisher,[3] which was recently applied in a therapeutic trial by Cattaneo, Lucchelli, Bona, and Maccacaro.[1] The technique was originally designed for use in classifying objects (e.g., mandibles of unknown sex) by means of a formula derived from measurements on objects whose classification was known (mandibles of known sex). As applied to two treatment groups after a drug trial, it answers the question "How successfully can the patients be identified as belonging to their respective groups by use of an index derived from a combination of all measures of effect?" The greater the ratio of correct to incorrect identifications, the stronger will be the conviction that the treatments have, in some respects at least, differed in their effects, and the greater will be the justification for further research, especially on the measures that contributed most to the discrimination.

The mathematical basis of the technique[6] is somewhat complex, but the general principle is clear. In terms of placebo- and drug-treated groups, the discriminant function is a special kind of "composite index" —the index which of all possible linear compounds of a set of measurements will best discriminate between two different groups.[3]

The index for each patient is formed by multiplying each of the measures (grip strength change, physician's rating, and so forth) by its appropriate weighting coefficient, and then adding the products together. The coefficients are calculated by a series of arithmetical steps, similar to the steps in multiple regression analysis from which the discriminant technique was derived; and the calculation insures two things:

1. The difference between the mean indices of the treatment groups is as large as possible in comparison with the differences between the patients' indices within the groups.
2. The contributions of the various measures are wholly, or to a very large extent, independent of each other, i.e., the confusing interrelationships of the measures are wholly or very largely removed.

As in regression analysis and analysis of variance, the differences among the indices are expressed as sums of squares of deviations from mean values. It is conceivable that some other measure of variation, with other weighting coefficients, would lead to better discrimination in some instances, but to discover such a method would require extensive exploration in each case.

Although the study of indomethacin is far beyond its early phase, it was of interest to inquire how much evidence this trial, by itself, would provide regarding a placebo-drug difference estimated from an optimal combination of all measures of effect. If there were only three measures, the arithmetic, shown in detail by Goulden,[4] would not be excessive for a desk calculator. In this trial a computer was employed and Goulden's worked example was used to test the program.

Three sets of discriminant functions (composite indices) were calculated, the numbers of patients differing in each set because only those that provided all the required measures could be used. The calculated values are here multiplied by 1,000 to avoid excessive decimal places. The plus and minus signs can be taken to represent, respectively, "improvement" and "deterioration," but what these words mean is obscure, as with all composite indices.

Set 1. Five measures: gradients (V1 to

V4) of active joint number, grip strength and duration of morning stiffness; physicians' and patients' scores (2– to 2+). Total patients: 101 (P, 50 and D, 51); median of total: 0.16+; total range: 19.02– to 20.88+; means: P, 1.92– and D, 1.01+; above median in P: 19 (38 per cent); below median in D: 19 (38 per cent).

This shows that, if one disregarded the actual treatments and classified all patients as "probably P" when their indices were below the median, and "probably D" when above the median, the frequency of misclassification in each group would be 38 per cent. Other dividing lines, above and below the median, gave similar and sometimes greater over-all percentages, because when the error in one group was reduced by a certain amount it was increased even more in the other group. Frequency distributions of the indices, with both groups in the same graph, illustrated clearly the lack of discriminatory power.

Set 2. Six measures: Set 1 with ESR gradient in addition. Total patients: 83 (P, 42 and D, 41).

Set 3. Seven measures: Set 2 with walking-time gradient in addition. Total patients: 73 (P, 34 and D, 39).

The results in these two sets were very similar to those in Set 1. The errors (misclassifications) by use of the median ranged from 36 to 40 per cent.

In view of the other reports on indomethacin it is quite possible that some of the "successes" in these classifications were actually due to benefits conferred by the drug on some patients. In looking at this trial by itself, however, one must ask: "If there were no real P-D difference in outcome, how often would the observed amount of discriminatory power be found?"

A direct answer to this question would be obtained by a randomization experiment —repeated shuffling of the data without reference to the therapies and a discriminant analysis after each shuffle. The common mathematical substitute for this experiment is the variance-ratio (F) test, in which the ratio is the variance between groups divided by the variance within groups. This test was applied as shown by Goulden[4] and the result for Set 1 (five clinical measures) was F = 1.41; degrees of freedom for the numerator, 5 (i.e., the number of measures) and for the denominator, 95. If there were no actual discriminatory power, this value of F, and greater values, would arise from sampling variation alone in 20 to 25 per cent of experiments. The F values in Sets 2 and 3 were, respectively, 1.15 and 1.47, with random frequencies slightly greater than in Set 1.

Therefore, even this sensitive method of combining observations would not suggest a superiority of drug over placebo.

Changes in one week after cessation of trial therapy (V4 to V5)

The changes that occurred in the week after capsule intake had ceased (and before the therapy assignments were revealed) were compared in the two treatment groups and compared also with changes reported during the 3 months of therapy.

Physicians' and patients' impressions. In the three periods (V1 to V2, V3 to V4, and V4 to V5) the percentage frequencies of patients who were reported as "unchanged" did not differ greatly, although the last interval was only a quarter the length of each previous interval. The three periods revealed no consistent P-D difference in these frequencies, which ranged from 49 to 62 per cent for the physicians and from 30 to 42 per cent for the patients.

In the patients who had been reported as changed during the medication period (V1 to V2 or V3 to V4), there was no clear suggestion of a P-D difference in the ratio of deterioration to improvement. In the V4 to V5 week, however, both the physicians and patients reported, among those who had manifested a change in that period, disproportionately higher frequencies of deterioration in the patients who had received the drug. (Physicians: placebo, 8 [38 per cent] of 21 patients; drug, 18 [75 per cent] of 24 patients; Pr from chi-square, 0.05 to 0.02. Patients: placebo, 8 [25 per cent] of 32 patients; drug, 22 [58 per cent] of 38 patients; Pr from chi-square, 0.02 to 0.01.) It appeared that the withdrawal of the drug had a detectably greater depressing effect than the withdrawal of the placebo.

Individual measures of disease activity. In patients who showed differences in readings between V4 and V5, the percentage frequencies of deterioration in joint numbers and grip strength were similar in the two treatment groups. (Number of clinically active joints: P, 29 [64 per cent] of 45 patients; D, 34 [68 per cent] of 50 patients. Grip strength: P, 28 [54 per cent] of 52 patients; D, 30 [54 per cent] of 56 patients.)

In morning stiffness and ESR the P-D differences were considerable. (Morning stiffness: P, 11 [32 per cent] of 34 patients; D, 27 [66 per cent] of 41 patients; Pr from chi-square, less than 0.01. Erythrocyte sedimentation rate: P, 15 [36 per cent] of 42 patients; D, 25 [56 per cent] of 42 patients; Pr from chi-square, approximately 0.1.)

In the analysis of magnitudes (mean values), in order to obtain comparisons of all four measures with each other, the patients from the clinic that reported doubt regarding ESR determinations were entirely excluded.

In all four measures in both treatment groups the correlations between the V4 to V5 changes and the V3 to V4 changes were negative, the coefficients ranging from –0.26 to –0.73 (with no consistent P-D differences). The mean V4 to V5 changes were, therefore, adjusted by estimation of what they would have been, according to linear regression equations, if the changes in the previous period (V3 to V4) had been zero. With numbers of patients per treatment group 45 to 49, the adjusted means (with negative signs indicating deterioration) were as follows: Number of clinically active joints: P, 1.28– and D, 2.26–; grip strength (millimeters Hg): P, 0.10– and D, 6.50–; morning stiffness (hours): P, 0.09+ and D, 1.10–; and ESR (millimeters in one hour): P, 0.37– and D, 2.08–.

The predominance of deterioration could conceivably be partly due, in the first three measures, to the patients' awareness that the special medication had ceased; but the data provide no way of testing that suggestion. In all four measures there was, on the average, greater deterioration in the D group than in the P group; however, except in morning stiffness, the differences were slight. They could well have been due to the randomization and cannot be accepted as independent confirmatory evidence, because there is some degree of correlation among the measures.

The average increase of one hour in duration of morning stiffness in D, as compared with a negligible change in P, calls for attention. Since the gains in the preceding (V3 to V4) period were almost identical (0.21+ for P, 0.19+ for D), the adjustment had little effect on the observed V4 to V5 difference (0.03+ for P, 1.21– for D); therefore, the latter could be used in the analysis.

The two-sample ranks test gave a Pr value of 0.01 to 0.02—more exactly, from interpolation in tables,[18] Pr = 0.0172, implying that a greater difference between the mean ranks for P and D, in favor of either treatment, would occur in approximately 1.72 per cent of randomizations. The difference was largely produced by 4 drug-treated patients whose duration of stiffness had increased to "all day" (arbitrarily counted as 16 hours), and their deterioration greatly exceeded the highest in the placebo group.

In evaluating this result it must be recalled that in the analysis of data in this trial many P-D comparisons of morning stiffness duration were made, and, even if randomization were responsible for all the differences, the occurrence of one Pr value slightly less than 0.02 would not be very surprising. This particular occurrence, however, can be taken in conjunction with the physicians' and patients' impressions of greater deterioration among drug-treated patients in the posttreatment week. Whatever the underlying phenomena of morning stiffness may be, the stiffness itself creates an awareness of ill-being, and it appears not unlikely that the same phenomena can create a feeling of depression, even if a question directed to morning stiffness itself reveals little or no change.

Comparison with total medication period. The V4 to V5 changes were compared, in direction and magnitude, with the V1 to V4 changes. The only well-defined P-D difference in this comparison was found in morning stiffness. In patients who improved in this symptom from V1 to V4, the frequency of deterioration from V4 to V5 was as follows: P, 5 (42 per cent) of 12 patients; D, 20 (91 per cent) of 22 patients; Pr from chi-square, less than 0.01.

In those patients who showed reversal of direction in V4 to V5, as compared with their direction in V1 to V4, the absolute amounts of change were compared in the two periods. The frequency of patients whose change in V4 to V5 was greater than their change, in the opposite direction, in V1 to V4, was as follows: Number of clinically active joints: 23 (46 per cent) of 50 patients; grip strength: 20 (36 per cent) of 56 patients; morning stiffness: 14 (42 per cent) of 33 patients; and ESR: 12 (26 per cent) of 46 patients.

Thus, of the patients who changed direction in the postmedication week, from one quarter to one half showed a greater amount of change than they had shown between the initial and final readings in the 3 month trial. There was no clear-cut difference in these frequencies between the P and D groups, or between the two types of reverse, "worse to better" and "better to worse," but the numbers in these subclasses were too small to demonstrate anything but a very large difference.

Table V showed that there were more and greater changes in degree of activity in the 3 month trial than in the one week variability study; but the figures just presented suggest that in a considerable number of patients the cycles of fluctuation (real changes and observational variation) are very short, and one may find as large changes in a week as in 3 months, or larger.

Undesirable nonarthritic symptoms

Withdrawals from the trial. Among the 7 P patients and 10 D patients who withdrew from the trial predominantly because of undesirable symptoms, the visits after which the patients withdrew were: V1 for 1 D; interim visit for 2 P and 2 D; V2 for 2 P and 4 D; and V3 for 3 P and 3 D. The alleged reasons for withdrawal in both P and D patients included: headache, dizziness, drowsiness, tiredness, nausea, vomiting, dyspepsia, and skin rash. Symptoms reported by some D patients, but not by P patients, were lightheadedness, mental confusion, and anorexia. The single commonest symptom was headache (in 2 P and 7 D).

It is not unlikely that suggestion influenced some of the patients, because the protocol contained the instruction: "Each patient is to be informed of the possibility of headache, dizziness, and gastrointestinal disturbances."

Patients who continued in the trial. The 109 patients who continued through the trial were questioned about undesirable symptoms from a list of twenty specific items on each visit, including the interim visit 2 weeks after V1; but in very few categories did a patient report a particular symptom on more than 2 of the 4 occasions available after the trial medications were started. Table IX shows frequencies of reports on one or more visits in patients for whom the particular symptom was reported absent on V1.

Individual symptoms. The frequency of untoward symptoms in placebo-treated patients illustrates the importance of such a control group and of a double-blind technique. Even with these precautions, it is not easy to estimate from Table IX the over-all adverse effects of the drug, for the following reasons. Although the frequency of symptoms in D exceeded those in P in all except 3 categories (vomiting, diarrhea, and edema), the other 17 P-D differences

Table IX. *Percentage frequency of undesirable symptoms during medication period. The denominators are patients (40 to 50 in each treatment group) who at visit 1 had reported absence of the symptom*

	Frequency (%) of occurrence reported on one or more visits		
Symptom	*Placebo*	*Drug*	*Difference (D – P)*
Headache	31.7	56.1	+24.4
Dizziness	24.4	50.0	+25.6
Lightheadedness	16.0	39.2	+23.2
Mental confusion	9.8	26.0	+16.2
Drowsiness	20.5	28.5	+ 8.0
Faintness	5.9	12.5	+ 6.6
Tiredness	30.0	32.0	+ 2.0
Anxiety or nervousness	25.0	33.4	+ 8.4
Anorexia	15.2	23.4	+ 8.2
Stomatitis	5.8	12.7	+ 6.9
Nausea	20.4	30.0	+ 9.6
Vomiting	9.4	7.6	– 1.8
Diarrhea	18.9	15.1	– 3.8
Abdominal pain	8.0	17.3	+ 9.3
Dyspepsia	16.3	22.4	+ 6.1
Edema	20.0	12.2	– 7.8
Tinnitus	21.6	31.7	+10.1
Blurred vision	18.3	20.4	+ 2.1
Skin rash	4.0	15.6	+11.6
Pruritus	10.4	15.6	+ 5.2

Headache was reported on more than 2 visits by 1 (2.4 per cent) of 41 P and by 9 (22.0 per cent) of 41 D. Dizziness was reported on more than 2 visits by 2 (4.4 per cent) of 45 P and by 6 (13.0 per cent) of 46 D.

cannot be taken as independent confirmatory evidence of general toxicity, because (1) some of the symptoms are physiologically correlated with each other, and (2) the protocol writers had tried to obtain full information by including all terms that had been used in previous reports on indomethacin, and this caused a risk of the same phenomenon being recorded in two or more categories.

It would also be difficult to decide, from these data alone, which differences were "probably real" and which were "probably fortuitous." The chi-square test of the P-D differences showed only three in which the random frequency (Pr) was less than 0.05—in headache (slightly less than 0.05), dizziness (slightly greater than 0.02), and lightheadedness (slightly less than 0.02). Without previous experience of the effects of the drug, these differences, although suggestive, would not have been very convincing because (1) even if all the P-D differences in the table had been fortuitous, three differences with this degree of "significance" would not have been very rare, and (2) the three symptoms in question are not entirely independent of each other.

Combinations of symptoms. A typical picture of indomethacin toxicity has been described as a combination of six symptoms—headache, dizziness, lightheadedness, mental confusion, nausea, and dyspepsia. Among the 10 D patients who withdrew before the trial was completed, only one was reported to have this collection of symptoms. In the records of the 109 patients who continued through the trial, 3 (5.7 per cent) of 53 P and 2 (3.6 per cent) of 56 D reported all these symptoms on one or more visits, although seldom all six symptoms on the same visit. When mental confusion was omitted, the figures for the remaining 5 symptoms were 4 (7.5 per cent) of 53 P and 6 (10.7 per cent) of 56 D. The syndrome could, therefore, hardly be called typical or specific.

In another combination, six items were grouped as belonging to the central nervous system: headache, dizziness, lightheadedness, mental confusion, drowsiness, anxiety or nervousness. Six other items were grouped as gastrointestinal: anorexia, nausea, vomiting, diarrhea, abdominal pain, and dyspepsia. In each group the patients were classified according to the total number of symptoms (0-6) reported on one or more visits after V1 (regardless of the presence or absence of the symptom on V1). Tinnitus, which might have been in the central nervous system group, was excluded because it is commonly associated with high aspirin intake. The remaining symptoms were not pooled because there is no obviously appropriate single grouping.

The results, expressed as percentage frequencies, in 53 P and 56 D are given in Table IX.

The P-D difference in the central nervous system group is clear, but in the gastrointestinal group even the apparently large difference in the present-absent contrast would not be rare in purely random assignments (Pr from chi-square, 0.2 to 0.1).

Among patients who reported neither pruritus nor rash on V1, 9 (21.4 per cent) of 42 D reported one or both of these on subsequent visits, whereas only 2 (4.7 per cent) of 43 P did so—a difference that would rather rarely occur by chance (Pr from chi-square, slightly less than 0.05).

Regarding all these P-D comparisons it should be noted, of course, that (1) the records did not contain any quantitative information on the intensity of symptoms, or even a day-by-day record of frequency, and (2) the frequency and intensity of symptoms induced by the medication (either physically or psychologically) would very probably be lessened by the patients' voluntary reduction of intake.

Laboratory tests

Methods. Blood urea nitrogen: phenolhydrochloride, diacetyl monoxime, thiosemicarbazone. Albumin in urine: sulfosalicylic acid turbidometric, Combistix (Ames Co.), Uristix (Ames Co.). Alkaline phosphatase: Bodansky, King-Armstrong, Sigma Chemical, Shinawara-Jones-Reinhart. Serum glutamic oxaloacetic transaminase: Babson, Reitman-Frankel.

Table X. *Percentage frequencies of central nervous system and gastrointestinal symptoms*

	Number of symptoms			
	0	*1-2*	*3-4*	*5-6*
Central nervous system				
P	32	40	19	9
D	14	32	32	21
Gastrointestinal				
P	53	28	15	4
D	36	39	20	5

Analysis. Patients whose reports showed that the levels were within "normal" limits on V1 were first classified according to whether they had or had not produced an "abnormal" reading on one or more of the subsequent visits (V2, V3, and V4); but this method of detection, appropriate in ordinary clinical care, is not the most satisfactory method in a search for drug effects during a trial, because (1) the limits of "normal" are arbitrary and may not be appropriate to individuals, and (2) an estimate of average change, utilizing all readings, reduces the effect of fluctuations and of observational variation. Therefore, "gradients" (rates of change per month) were estimated from the readings on all four visits (V1 to V4), as for the data on clinical activity measures. Here again, a gradient does not imply clinical or statistical significance; it is simply a measure for use in the comparison of the P and D groups.

Since the numerical values of the gradients varied according to the laboratory method, attention was confined to the direction (positive or negative) of the gradients.

The group totals of patients in this section are smaller than in preceding sections, because all data from one clinic were excluded as of questionable reliability.

Results. "Above normal in trial" refers to patients whose readings were within normal limits on V1 but were above the upper limit on one or more of the subsequent visits.

White blood count. Normal limits: 5,000 to 10,000 per cubic millimeter; above normal in trial: 11 of 45 P, and 11 of 43 D (highest value, 12,300 in P); below normal in trial: 4 P, and 3 D. Gradients (87 P and D): positive, 40 per cent; negative, 60 per cent (Pr of difference from 50 per cent, approximately 0.05).

Blood urea nitrogen. Normal limits: 0 to

20 mg. per 100 ml.; above normal in trial: 5 (11 per cent) of 45 P, and 17 (37 per cent) of 46 D (Pr from chi-square, less than 0.01); highest levels: 25 mg. in 2 P and 29 mg. in 1 D. Gradients: zero in 1 (P); positive, 24 (53 per cent) of 45 P, and 34 (74 per cent) of 46 D (Pr from chi-square, 0.07).

Since vomiting and diarrhea can cause an increase of blood urea nitrogen levels, the P-D comparison was repeated on the data from patients (41 P and 40 D) who were reported free from these two symptoms on all visits after V1; the result was unchanged.

Albumin in urine. No patient was reported as having more than a trace of albumin in the urine. Among patients reported free from albumin on V1, 7 of 39 P and 8 of 39 D were reported as having a trace on one or more subsequent visits. There was no suggestion of an association between abnormal blood urea nitrogen levels and the presence of traces of albumin.

Serum alkaline phosphatase. Ranges of normal were supplied by clinics. Above normal in trial: 4 (10 per cent) of 39 P, and 9 (26 per cent) of 35 D (Pr from chi-square, 0.2 to 0.1). Gradients among patients within normal limits at V1: zero (equally balanced fluctuations) in 2 of 39 P, and 2 of 35 D; positive, 17 (46 per cent) of 37 P, and 26 (79 per cent) of 33 D (Pr from chi-square, slightly greater than 0.01).

Serum glutamic oxaloacetic transaminase. Normal limits: 6 to 40 units per milliliter; above normal in trial: 5 of 43 P, and 5 of 45 D. Gradients: zero in 1 (P); positive, 22 (51 per cent) of 43 P, and 19 (43 per cent) of 44 D.

Summary. In white blood count, serum glutamic oxaloacetic transaminase, and urinary albumin levels there was no suggestion of a real P-D difference with reference to clinical norms or in gradients (average rates of change). In blood urea nitrogen and alkaline phosphatase levels, the placebo patients showed changes consonant with normal fluctuation and observational variation (a 50:50 ratio of rise and fall), but the readings in the drug-treated patients showed a distinctly greater tendency to rise than to fall.

Although the effects were apparently of no immediate clinical significance, it is impossible, from a sample of this size, to make reliable estimates of how many patients might be similarly affected, and to what degree, if the drug were similarly administered to a much larger group of patients.

Dose-response relationships

When the dose of a drug is varied by the physician or patient in accordance with apparent response to therapy, or because of undesirable symptoms, simple dose-response inferences are not valid. It is desirable, however, to see what relationships appear to hold between drug intake and changes in the patient's condition.

Intake of capsules. At each of four visits (V1, interim, V2, and V3) the bottle given to the patient contained enough capsules for the ensuing period, and was supposed to contain also capsules for 3 additional days; but capsule counts of bottle contents before use revealed errors up to 5 capsules under or over the supposed numbers.

The figures used in the study of dose relationships were estimates based on counts of capsules remaining in the bottles returned on V3 and V4, and covering the last 2 months of the trial, during which the scheduled total intake was 392 capsules. Because of the variation in bottle contents the estimates might be in error by ± 10 capsules (5 for each bottle), in addition to errors due to miscounting and capsule loss. The 27 patients (10 P and 17 D) who did not return bottles were asked to estimate their remaining capsules, but these figures were not used in the final analyses, which are, therefore, derived from 43 P and 39 D patients.

Attention was paid chiefly to data from patients whose 2 month intake could be classified as definitely below schedule, the arbitrary cut-off point being 375 capsules, i.e., 17 less than 392—approximately 2 days' dose (16 capsules) during the last month of the trial. In the class so defined there were 17 of 43 P and 20 of 39 D. The three lowest estimated intake values were in P: O,[*] 31, and 82; in D: 52, 114, and 120.

Relationship to undesirable symptoms. The records of the 17 P and 20 D patients were examined for explanations of the decreased intake. There were no comments in 8 P and 6 D. Forgetfulness was the alleged reason in 3 P and 2 D, but in 6 P (35 per cent) and 12 D (60 per cent) there was evidence of association with disagreeable symptoms. The P-D difference might be fortuitous (Pr from chi-square, 0.3 to 0.2), but it is more likely that it reflected drug-induced symptoms.

In the same groups of patients, correlations were sought between the estimated capsule intake and total undesirable-symptom scores, which were formed by giving a point for each occurrence of any one of the twenty undesirable symptoms (the maximum possible score for V3 plus V4 was 40). It was conceivable that undesirable symptoms in the first month (interim visit and V2) would influence the drug intake during the next 2 months (V3 and V4); therefore, the two time periods were considered separately. The four Spearman's coefficients of correlation with V3 plus V4 intake estimates ranged from –0.04 (D, first month's symptoms) to –0.38 (P, last 2 months' symptoms).

The relationships were all in the expected direction (more symptoms, lower intake) but the values were small, and all of them, as well as the P-D differences and the differences between the two periods, could well be fortuitous.

Relationship to disease activity. In patients whose estimated intake of capsules during the last 2 months of the trial was at or near the scheduled level, there was no discernible relationship between capsule intake and the changes in numbers of clinically active joints during those two months (V2 to V4). Therefore, attention was concentrated on patients whose estimated V3 and V4 intake was less than 350 capsules—11 P (10 in ESR) and 12 D (10 in ESR). The product-moment correlation coefficients between capsule intake and measures of disease activity are given in Table XI.

These coefficients are not high and none of them would be rare in a randomization experiment; but if all of them had been obtained from groups of drug-treated patients it could have been plausibly argued that, even though not "statistically significant," they probably indicated improvement "caused by" greater intake. This is an example of the dangers of facile dose-response inferences.

Aspirin consumption as a measure of drug effect

Patients' daily consumption of aspirin has been used by some investigators as a measure of the effectiveness of other drugs in rheumatoid arthritis but without much attention to factors that might influence its validity. The Committee has not used this method of assessment, partly because one or two of the clinics try to develop in their patients a habit of maintaining an assigned dose level and are unwilling to allow the habit to be broken. Moreover, to make aspirin intake even a moderately precise measure, a kind of "titration to comfort" experiment would be required—instruc-

Table XI. *Product-moment correlation coefficients between capsule intake and measures of disease activity*

Measure	*P*	*D*
Number of clinically active joints	+0.35	+0.37
Grip strength	+0.45	–0.01
Morning stiffness	+0.37	+0.31
ESR	+0.13	+0.17

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[*] This patient had ceased taking capsules after V2, due to undesirable symptoms. Although she had not actually withdrawn from the trial, she ought perhaps to have been included in the list of withdrawals, but the zero intake was not noted until much of the analysis had been completed.

tions to take aspirin until symptoms were relieved, but no more, and to keep accurate daily records. To be reliable, such an experiment would have to be confined to selected patients or to hospital patients under constant supervision. In this trial aspirin consumption data were analyzed with reference to possible fallacies.

On each assessment visit the patients were asked to state how many aspirin tablets (or in some cases amounts of sodium or other salicylate) they had taken the previous day and to give the brand names (about two dozen). All values were converted, by reference to manufacturers' statements, into equivalent 5 grain tablets of acetylsalicylic acid. Patients who on V1 had reported 2 tablets or fewer were excluded from the analysis, as were all patients at one clinic where maintenance of a stipulated minimum intake was apparently attempted. From the four monthly reports the gradients (average monthly rates of change in one day's number of tablets) were estimated, as for the measures of clinical activity (Table XI).

One might multiply the means by 3 and say that, if the slopes had been straight throughout the trial, the drug-treated patients would, on the average, have been consuming 4 fewer tablets per day at the end than at the beginning, whereas in the patients taking placebo the average diminution would have been only one tablet.

These are small values and the P-D difference is small, but it would rarely occur by chance (Pr from the two-sample rank test, 0.02 to 0.01). It would, however, be quite illegitimate to accept this as a proof of benefit from the drug without considering other explanations. For example, the more frequent disagreeable symptoms in the D group might have prompted some patients to reduce their intake not only of trial medication but of aspirin also.

Undesirable symptoms were relatively frequent in patients whose trial medication intake was classified as "subschedule," either from counts of bottle contents on V3 and V4 (fewer than 375 capsules in 2 months) or from patients' reports when counts were not obtainable.

Table XII. *Gradients of aspirin intake*

	No. patients	*Range*	*Median*	*Mean*
P	36	−2.8 to +2.2	0.0	−0.31
D	42	−5.6 to +1.2	−1.2	−1.27

Table XIII. *Symptom scores and aspirin consumption gradients*

	Symptom scores			*Correlation with aspirin gradients*
	Range	*Median*	*Mean*	
P	0-28	8	8.3	−0.48
D	0-56	14	16.6	−0.20

This group (15 P and 22 D) showed a slightly greater P-D difference in mean aspirin gradient than did the total. (Mean gradients: P, +0.03 and D, −1.11; the difference = 1.14.)

In this group an undesirable symptom score was obtained by a point system as described under section on Dose-response relationships (maximum possible score after V1 = 4 × 20 = 80). Then product-moment correlation coefficients were obtained (Table XIII).

The coefficients, being negative, show that on the average a higher symptom score was associated with a greater diminution (or smaller increase) in aspirin intake. In samples of this size the relationship might be fortuitous, but it was legitimate to ask how much of the observed P-D difference in aspirin gradients (1.14) was associated with the difference in symptom score—more specifically, to ask what might the P-D difference have been if both groups had the same mean symptom score (e.g., 12, about half-way between the observed scores). The linear regression estimates of the "adjusted" mean gradients were: P, −0.24 and D, −1.04; the difference = 0.80, as compared with the difference before adjustment, 1.14.

It is not certain how far a t-test verdict is reliable with such data, but in this case the interest was in a comparison of the adjusted with the original values, not in the absolute probability values (Pr). The Pr values from the t test were: for the original P-D difference (1.14), less than 0.01 and for the adjusted difference (0.80), between 0.05 and 0.02. Thus, even a rather crude method of allowing for the relationship between untoward symptoms and aspirin consumption reduced considerably the strength of the apparent evidence in favor of a P-D difference. Obviously, aspirin intake ought not to be accepted as a measure of drug effect, even in a "titration to comfort" experiment, without a careful search for fallacies.

Intake of tranquilizers and sedatives

Patients' records were divided into two classes: (1) those who had, on questioning, reported throughout the trial no consumption of nontrial medication except salicylates (and sometimes vitamins)—34 P, 35 D; and (2) those who had taken tranquilizers, propoxyphene hydrochloride (Darvon), or sedatives frequently throughout the trial—5 P, 7 D. The groups were compared with respect to the gradients of the five measures of clinical activity. With such small numbers in the second group, differences would have to be large to be convincing, but there was not even a suggestion of a relationship between these supplementary drugs and the response to the trial medications.

Discussion

Comparison of the two treatment groups in this trial showed no justification for choosing indomethacin with aspirin in preference to placebo with aspirin. None of the recorded pretrial characteristics of the patients indicated which of them would be most likely to benefit from the drug. There was an excess of undesirable nonarthritic symptoms in the drug-treated patients, but their frequency was rendered somewhat less impressive by the occurrence of the same symptoms in some placebo patients.

It might be asked whether more refined techniques of analysis would not have revealed a more clear-cut drug-placebo difference. When the draft of this report was circulated for comments, the following suggestions for increasing the sensitivity of the comparison were received:

1. "One-tailed" tests of statistical significance.
2. "Ordered chi-square" instead of "ordinary chi-square" in tables with graded scores.
3. Analysis of quantitative measures as such, instead of reduction to quantal scores, which ignore the degree of change.
4. Calculation of weighted estimates of placebo-drug differences, taking into account interclinic differences in variability and lack of agreement with respect to treatment differences.

Some efforts of this kind may be appropriate in an early phase of drug testing, where it is desirable to seek from very small samples as much evidence as possible to justify more extensive investigation. In relation to the present trial the proposals suggest a great desire, for some reason or other, to demonstrate a "significant" difference—to disprove a null hypothesis. The Committee's objective was not to test such a hypothesis. Even if the proposed techniques produced numerous "significant" differences (although the data show little likelihood of this), these verdicts would not alter the observed small degree of benefit attributable to the drug under the conditions described. Two of the proposed techniques, however, call for specific comment.

The "one-sided" or "one-tailed" test is, in this context, a device whereby a Pr value of 0.10 to 0.05, in favor of a drug, is halved and recorded as 0.05 to 0.025. Thus, if the chosen cut-off point (significance level) is 0.05, a difference that was "not significant" becomes "significant." It is argued that the test is appropriate to answer the question "Are the clinical responses better with the drug?" whereas the original (two-sided) test answers the question "Are the responses on P and D different?" The one-sided test implies, however, that even a very large difference (with a very small Pr value) in favor of placebo would have to be attributed solely to the randomization of treatments—that the drug under test could not possibly give less benefit than placebo treatment. It is questionable how many thoughtful investigators would accept this belief.

The question of interclinic differences, in variability and in responses to therapy, always arises in multiclinic trials. Presumably such differences always exist, not only between clinics but also between observers at the same clinic and between various other subgroups into which patients might be divided—even down to individual patients. In the 7 day variability study[2] there were distinct interclinic differences in the degree of clinical activity of patients on day 1; but when the changes from day 1 to day 8 were examined in the ten initial-severity classes, no marked or consistent interclinic differences were found. That is one reason why that classification was used in the analysis of the indomethacin trial data.

In that trial the randomization of treatments had been complete, without any attempt to equalize the P and D numbers within the clinics, Therefore, it was legitimate to compare the treatment groups without stratifying by clinics. Within the clinics the interpatient variability in outcome was great, and scrutiny of the figures did not reveal any consistent interclinic differences in response. Even if convincing differences had been found, they would have served only to emphasize the uncertainty of the therapy when applied by different competent observers who followed a uniform procedure.

Summary

Without questioning the possibility that indomethacin benefits some patients, this 3 month, 11 clinic, completely blindfold trial, with random assignment of placebo and drug, studied arthritic symptom changes and the frequency of undesirable nonarthritic symptoms in patients with nonjuvenile peripheral rheumatoid arthritis, of both sexes and of widely diverse age, duration of disease, degree of clinical activity, and rheumatoid-factor titer. The daily doses of the drug, in capsules, were increased by schedule from 50 to 200 mg. Salicylates were permitted to both groups.

Assessment, at monthly intervals, was made by five relatively objective measures (number of clinically active joints, grip strength, duration of morning stiffness, erythrocyte sedimentation rate, and 50 foot walking time), by physicians' and patients' impressions, by the American Rheumatism Association functional classes, and by responses to a twenty item list of undesirable nonarthritic symptoms.

Out of 136 qualified patients, 27 (12 P, 15 D) withdrew during the trial. In both groups the alleged reasons were chiefly undesirable symptoms and worsening of the arthritis.

In the remaining patients (53 P, 56 D), the differences between initial and final visits in the first four objective measures were evaluated by reference to the ten severity classes, derived from the Committee's 7 day variability study, which permitted correction for initial level of clinical activity, and a matched comparison of P and D groups. The frequencies of change (improvement or deterioration) were very similar in both groups.

Gradients (average monthly rates of improvement or deterioration) were estimated for the five objective measures. In both treatment groups the average gradient in each measure differed little from zero, and the interpatient variation in gradients, although large, was similar in both groups. Subdivision by sex, age, disease duration, and rheumatoid-factor titer revealed no greater evidence of a P-D difference than did the undivided data.

No suggestion of a real P-D difference

was revealed by the over-all impressions of physicians or patients, by changes in functional class, or by the combination of all objective and subjective measures by an optimal weighting technique, the discriminant function.

Undesirable (nonarthritic) symptoms, most notably, headache, dizziness, and lightheadedness, were more frequent in the drug-treated group, but this difference was rendered somewhat less impressive by reports of the same symptoms in some patients taking placebo.

Changes in white cell count, serum glutamic oxaloacetic transaminase, and urinary albumin were similar in both groups, but in the drug-treated patients blood urea nitrogen and serum alkaline phosphatase levels showed a distinctly greater tendency to rise than to fall, whereas patients or placebo showed about equal frequencies in both directions.

One week after trial medication had ceased, and before treatment assignments had been revealed, physicians' and patients' impressions recorded a much higher frequency of deterioration in the D than in the P patients. The average duration of morning stiffness reflected the same difference.

The following pitfalls in inferences from such trials are illustrated and discussed:

1. The danger of failure to recognize the subordinate, and limited, role of statistical "significance" tests.

2. An inevitable degree of uncertainty regarding the type of patient to whom the results were applicable, owing to selection effects: (a) exclusion of patients who have previously received the drug, and (b) the complex factors that prompt a patient to withdraw from a trial.

3. The greater frequency of improvement than of deterioration in both treatment groups, illustrating the importance of controls (contrast groups or switch-back design).

4. Fluctuation of symptoms, with negative correlations between changes in two successive periods in the trial—a source of serious error if change of therapy is determined by current symptoms.

5. The fallacy of dose-response inferences, illustrated here by positive correlations, in both treatment groups, between improvement and numbers of capsules consumed.

6. The unreliability of intake of another drug as a measure of the effect of a test drug. There was a small P-D difference in the estimated average rate of change in aspirin intake, but the reliability of this observation was greatly reduced by correction for the association between aspirin intake and untoward (nonarthritic) symptoms.

The following is a list of the clinics and observers involved in this trial. Southwestern Medical School, Dallas: Drs. J. L. Ferguson, W. L. Norton, and P. Stastny. State University of New York, Downstate Medical Center, Brooklyn: Drs. D. A. Gerber and D. Kaplan. University of Illinois, Chicago: Drs. J. C. Kulis and L. Penev. University of California and Veterans Administration Hospital, Los Angeles: Drs. R. A. Jensen, W. H. Pitts, and J. C. Soucy. Massachusetts General Hospital, Boston: Drs. L. Miller, J. A. Mills, R. S. Pinals, D. Robinson, and M. Ruderman. Jackson Memorial Hospital, Miami: Drs. H. E. Brown, Jr. and A. R. Portuondo. Rackham Arthritis Research Unit, University of Michigan, Ann Arbor: Drs. W. J. Bushnell, W. M. Mikkelsen, and M. P. Strottmann. Presbyterian Hospital, New York: Drs. C. L. Christian, W. B. Hatfield, A. I. Snyder, and E. A. Wheaton, Jr. University of California, San Francisco: Drs. F. Ferraris and I. E. Shalit. University of Tennessee, Memphis: Dr. D. McC. Mills. University of Washington, Seattle: Drs. L. A. Healey and R. F. Willkens.

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Senator NELSON. Doctor, we are grateful that you were willing to take the time to come here today. You may present your statement as you desire.

STATEMENT OF DR. WILLIAM M. O'BRIEN, ASSOCIATE PROFESSOR OF PREVENTIVE AND INTERNAL MEDICINE, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE, CHARLOTTESVILLE, VA.

Dr. O'BRIEN. Senator Nelson, members of the subcommittee, and guests, before I begin my testimony I would like to clearly state that the views which I express are my own and in no way represent those of the University of Virginia School of Medicine where I am employed. In addition to my salary at the University of Virginia, during the past year I have earned $650 in consulting fees from the National Center for Chronic Disease Control, Consumers Union of the United States, and the Medical Letter. I have no other source of income or support. I do not receive honoraria or grants from either the drug industry or the Food and Drug Administration.

My education and qualifications are:

M.D., Yale University, 1956.

Intern and assistant resident in medicine, Massachusetts General Hospital, 1956–58.

Clinical investigator, National Institute of Arthritis and Metabolic Diseases, 1958–64.

Assistant professor of epidemiology and internal medicine, Yale University School of Medicine, 1964–67.

Associate professor of preventive and internal medicine, University of Virginia School of Medicine, 1967 to the present.

My field of interest is in rheumatic diseases and I have participated in drug studies on the treatment of rheumatoid arthritis and other rheumatic diseases since 1958. I am a member, or more strictly speaking, an employee, of the Cooperating Clinics Committee of the American Rheumatism Association and assist in design and analysis of their drug trials. I have published 29 scientific papers on the natural history and treatment of rheumatic diseases.

I wish to make statements concerning three subjects: the evaluation of clinical trials of indomethacin, the toxicity of indomethacin, and the advertising of indomethacin and other drugs.

I. CLINICAL TRIALS OF INDOMETHACIN

Indomethacin was first reported as an anti-inflammatory drug in 1963. During the past 4 years I was involved in several trials of indomethacin. I felt there were many lessons to be learned from these experiences and prepared a history of all published clinical trials of the drug. (Exhibit No. 1.)[1]

The 1962 Kefauver-Harris amendments specifically stated that a manufacturer must support claims of efficacy of a drug with "substantial evidence." The law defines this as "adequate and well controlled investigation by experts qualified by scientific training and experience to evaluate effectiveness."

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[1] Exhibits 1–5 submitted by Dr. O'Brien begin at p. 2827, infra.

I define the word "control" as a standard of comparison for checking inferences in an experiment—in other words, in testing a drug one group is treated, and its response is compared to the response of an identical group which receives a dummy (placebo). I believe this was the exact intent of Congress in the 1962 amendments. By mid-1965 the Food and Drug Administration officials thought that clinical trials of indomethacin presented to them satisfied these criteria, and released the drug for general use.

By 1967 about 24 clinical studies of indomethacin giving sufficient detail for analysis had been published in the medical literature. Of these, 18 were subjective evaluations; namely, that the patient was simply asked whether he felt better or worse. Authorities on drug testing have warned repeatedly of the fallacy of subjective, uncontrolled evaluations. The danger lies in the "placebo effect." A chronically ill patient is depressed and neglected, then suddenly he is told he is to receive a wonder drug, and his doctor takes a new interest in his wellbeing and gives him every attention. Many scientific studies have shown that this effect is due to relief of the anxiety, fear, and despair which accompany chronic disease, and due to the extreme optimism of physicians about a new remedy. The subjective uncontrolled evaluations reported 61.8 percent of patients had good or excellent responses to indomethacin.

By 1967 six studies which used some objective evaluation of patients such as grip strength, number of painful and tender joints, and so forth had appeared. Experts in clinical testing have also recognized that these objective uncontrolled trials may result in errors. Rheumatoid arthritis is a very variable disease and often cures itself. Spontaneous remissions occur frequently, and in an uncontrolled trial these remissions may be attributed to benefits from the drug rather than the natural history of the disease. Further, doctors usually start their patients on drugs when they are getting worse. Rheumatoid arthritis is a cyclical disease with periodic ups and down. Obviously, a drug is likely to be started when a patient has gone through a period of deterioration and chances are the patient will soon show improvement. This improvement may be due to the cyclical nature of the disease, rather than benefits from the drug. These objective uncontrolled trials of indomethacin reported 25.1 percent of patients with rheumatoid arthritis showed improvement.

In early 1967, four carefully controlled double-blind trials were published. These careful scientific experiments, which compared response of patients given indomethacin to responses of carefully matched controls given either placebos or standard aspirin therapy, indicated that indomethacin is no more potent than aspirin. The results of these trials were drastically different than previous assessments of this drug. Although over 300 clinical studies of indomethacin had been done in the past 5 years, only four (at most eight), would qualify as careful well-controlled experiments.

Mr. GORDON. May I interrupt you for a moment? On page 2 you say, "Authorities on drug testing have warned repeatedly of the fallacy of subjective uncontrolled evaluations." Can you cite some of these?

Dr. O'BRIEN. An example is Dr. Mainland's textbook on Elementary Medical Statistics. Perhaps someone who has even been more concerned about this is Sir Arthur Bradford Hill, the great English statistician. He documents this extensively in his book Principals of Medical Statistics, and his writings on clinical trials.

When indomethacin was released——

Senator NELSON. Excuse me, Doctor.

The last sentence you read was that only four or at most eight of these clinical studies would qualify as careful, well-controlled experiments. Do you discuss the results of these four or eight studies?

Dr. O'BRIEN. The results are discussed in exhibit 1 and summarized in the first table, Senator. There are some very minor defects with some trials. I would say none of them were absolutely perfect but this is the only substantial evidence which has ever been presented concerning indomethacin which is totally or relatively without bias.

Senator NELSON. And what do they demonstrate as to the effectiveness of Indocin in cases of rheumatoid arthritis?

Dr. O'BRIEN. In our trial, we could not distinguish indomethacin and placebo from aspirin and placebo. The other trial was Pinals, who will testify tomorrow. He could not distinguish between indomethacin and aspirin. Another major trial is that of Sharpe from the University of Manchester, England. He could not distinguish between indomethacin and aspirin. There are a few other trials worthy of note, by Ward of Salt Lake City, Pitkeattly of Manchester, and by Percy of Newcastle, England. All failed to indicate that this drug could be distinguished from aspirin.

Senator NELSON. These experiments that you are referring to were limited to rheumatoid arthritis patients only?

Dr. O'BRIEN. That is right. Very few controlled trials of indomethacin have been published in other circumstances. Vignan and his associates have published a careful trial on rheumatic fever indicating the drug has no use there, and in June in the Canadian Medical Journal, T. D. Kinsella has published a carefully controlled trial on ankylosing spondylitis, reporting indomethacin relieves some of the pain but did not affect any objective measures in this disease.

Senator NELSON. I notice that one of the ads lists indications of Indocin for symptomatic treatment of rheumatoid arthritis, ankylosing spondylitis, degenerative joints diseases, osteoarthritis of the hip and gout. What about gout? Have there been objective clinical trials on that that have been published?

Dr. O'BRIEN. No controlled clinical trials that I am aware of. I am aware of one controlled trial by Wanka and Dixon on osteoarthritis of the hip.

Senator NELSON. What did that demonstrate?

Dr. O'BRIEN. That demonstrated some analgesic effect, but Michotte has also seen that there was some analgesic effects, but the drug did not affect the progression of the diseases. Those references are documented in exhibit 1. I think the exhibit will be published so anyone can refer to that.

Senator NELSON. Please go ahead, Doctor.

Dr. O'BRIEN. When indomethacin was released in 1965 it was hailed as "drug of the year." The physicians who used this compound believed they were giving their patients a wonder drug which would bring relief to most sufferers. Physicians who had done uncontrolled tests stated publicly, "Indomethacin * * * appears to be more effective than any other anti-inflammatory drug for long-term management" and, "The high percentage of good and excellent results in nonrheumatoid benign rheumatic diseases suggests that it is the drug of choice," and advertisements carried glowing testimonials from these doctors. (Exhibit No. 2.)

Mr. GORDON. When an advertisement says that this drug or any drug can be considered a drug of choice, would you not assume from that that comparisons had been made with other drugs?

Dr. O'BRIEN. Yes; I would think that if you are going to say it is the drug of choice—namely, the best drug to be used in treating a disease—that you would have to compare it with other drugs and in fact these doctors who claimed it was the drug of choice had not done this.

Mr. GORDON. Thank you.

Dr. O'BRIEN. At the request of this subcommittee, I was allowed to examine the Food and Drug Administration's records on indomethacin. At the time at which the Food and Drug Administration approved this drug, they had available approximately 137 studies. None of these studies were controlled double-blind trials and 134 had no controls of any kind.

Mr. GORDON. Do you have any idea of how many volumes there are to support the New Drug Application?

Dr. O'BRIEN. There are over 100 volumes. There were 26 volumes at the time the drug was approved.

Mr. GORDON. And you inspected the 26 volumes?

Dr. O'BRIEN. I inspected the 26 volumes in detail.

Mr. GORDON. And any other volumes besides those?

Dr. O'BRIEN. I inspected other volumes which were of specific interest after that.

Senator NELSON. You say 26 volumes. What do you mean by that? What is a volume?

Dr. O'BRIEN. A volume is about half the size of a Manhattan phone book. The records on indomethacin can be, of those 26 volumes, could be compared to the old recipe for chicken soup where you take one chicken and a carload of noodles: One page of analysis and a carload of very complicated forms. It certainly takes a great deal of work to wade through these volumes and I have the greatest respect for the officials of FDA who do so. I would say the official of FDA who reviewed these records reviewed them with great care. I did not reach the same conclusion as that official but certainly the official was very diligent in carefully going through each of these records.

Senator NELSON. Would you wish to say what your judgment of this application would have been had you been the one responsible for deciding whether or not it was acceptable?

Dr. O'BRIEN. I will come to that, but I would say on the basis of the information submitted to me I would have rejected it because it did not comply with the 1962 amendments which require controlled studies, assuming that my definition of control is the proper one.

Of these studies, 52 or 38 percent involved nine or fewer patients, and only six investigators had experience with more than 90 patients. The vast majority of case reports were brief notes on 1-page forms, and none contained careful statistical analyses of results.

The report which swayed the official of the Food and Drug Administration more than any other was the highly subjective double-blind study of Rothermich which was accepted by the Food and Drug Administration as a single-blind study. This study has since been published in the Journal of the American Medical Association (vol. 195:1102, 1966). The study is highly biased and the public report states "placebo was introduced whenever the patient seemed to be established and well controlled on indomethacin therapy." Since the disease is cyclical, introducing a placebo when a patient was doing well would probably be followed by a relapse. A study of this type was designed in such a way that the bias is in favor of the drug. Under these circumstances, it is very unlikely that anything other than a good therapeutic response would be observed, and Rothermich reported 75 percent of his patients improved. Although a crossover technique was used in switching drug and placebo, no crossover analysis was done. The crossovers were done in an arbitrary fashion, and doses were increased to levels of 500 mgms/day, about three times the maximum safe dose. The two other trials using placebos were also biased in favor of the drug.

This study of Rothermich, as submitted to the Food and Drug Administration, differs drastically from the manuscript that was published in the Journal of the American Medical Association. The author deleted the double-blind trial in the journal article, and only uncontrolled observations were published. None of the six largest studies were ever published in scientific journals.

Senator Scott. Right there, Doctor, you use the word "presumably" and yet you were speaking recently about being objective. Now, when you say that the editors "presumably" felt this portion was scientifically invalid and would not publish it, is that an objective or subjective statement by you?

Dr. O'Brien. Well, Senator, it appears to me that I knew the people who reviewed the manuscript and rejected it the first time.

Senator Scott. Now, we have the word "apparently" instead of "presumably." Are you saying in effect that you know that certain people made certain tests and you do not trust those people or do not trust their judgment? What is it you are trying to tell us?

Dr. O'Brien. I think the manuscript was submitted to the Journal of the American Medical Association and they rejected the manuscript because they felt it was scientifically invalid. The manuscript was then modified and it was published in a modified form. The point is that this is supposedly a double-blind control trial and yet a scientific journal only publishes it as an uncontrolled trial. This would indicate that there were in fact other people who would agree with my evaluation that this is an uncontrolled trial and this is the point I am trying to make.

Senator Scott. Go ahead.

Dr. O'Brien. In summary, the Food and Drug Administration in 1965 was confronted with 137 uncontrolled studies involving several thousand patients. Only three studies had controls, and all were biased in favor of the drug. The Food and Drug Administration officer reviewing the application in January 1965, stated:

> Although there is a paucity of controlled studies in this massive NDA, it is apparent that many patients with rheumatoid spondylitis and gout and some

patients with rheumatoid arthritis receive significant benefit from the anti-inflammatory effects of this drug.

Their officials were aware of the biases in some of these uncontrolled trials. In other instances they did not identify defects in the trials. They apparently felt, however, that the sheer weight of numbers overcame these biases and approved the application. They apparently felt optimistic that the newly introduced capsules would produce less toxicity than the older tablets. (Recent reports have indicated that the capsules are probably as toxic as the tablets.) Finally, they acted on the drug without any consultation with outside experts in the field of treatment of rheumatic diseases. The drug was thus released to the medical public based on studies which greatly overestimated the efficacy of the compounds. The medical public used the drug thinking it was a panacea.

Senator SCOTT. Doctor, you have quoted the Food and Drug Administration in 1965 as if that were the only finding to the effect that many patients with gout and rheumatoid arthritis have received significant benefits. May I call your attention to an article in the Bulletin on the Rheumatic Diseases, December 1967, volume 18, No. 4, by Dr. L. A. Healy, of Seattle, Wash. The bulletin is published by the Arthritis Foundation. I am sure you are familiar with the statements in this article which support the findings of the Food and Drug Administration in January 1965.

For example—

> Indomethacin is very effective in the treatment of a gouty arthritis—

And it cites Smyth and others. It goes on—

> Although they felt that indomethacin was preferable to phenylbutazone or colchicine in their patients, most observers regard the drug as equally effective in gout. Either indomethacin or phenylbutazone is preferable to colchicine for acute attacks of known or proven gout, since the distressing nausea and diarrhea that accompany the traditional hourly colchicine tablets can be avoided. The possible value of daily indomethacin in preventing recurrent attacks of gouty arthritis has not been assessed.

Dr. Healy's paper also mentions that indomethacin often relieves the pain of degenerative hip disease but has no effect in ailments of a similar type of treatment, and so on. Here it is 2 years later such a statement is made. May I ask why you did not include that in your statement?

Dr. O'BRIEN. Well, I am coming to this chronologically, Senator, but I would like to point out that when the application was approved in 1965 based on these 137 studies in rheumatoid arthritis, there was a paucity of controlled trials, at best one, and many people would not accept this.

Senator SCOTT. By 1967 there had been a great many more controlled trials, that is——

Dr. O'BRIEN. By 1967 there had been at least four controlled trials which could not distinguish between this drug and aspirin. And, I think it is fair to say that in 1967 there were controlled studies of this drug in ankylosing spondylitis which could not show it had any great benefit. As far as I know, no controlled studies have ever been done in gout. The only controlled studies done in osteo-arthritis have shown that it relieves the pain but does not prevent the progression of the disease.

Mr. Gordon. Dr. Rothermich also says in the same article:

"For this reason, from the statistician's viewpoint, the placebo trials in this report"—Dr. Rothermich's—"and probably in most clinical drug reports, cannot be considered as true blind studies."

For the record, will you please compare and contrast the use of the placebo trials in his report with the true blind studies used in your 11-clinic trial?

Dr. O'Brien. Well, I think that Dr. Rothermich committed fallacy so well described by Sir Arthur Bradford Hill (New England Journal of Medicine 247:113, 1952), of the free-for-all experiment in the circular reasoning, that one gives indomethacin until one gets a response. He starts the drug when the patient is doing poorly and then he waits for a so-called maximum benefit, and then he withdraws the drug and the patient gets worse. If the disease has its ups and downs, one can get into some very fallacious reasoning by using indomethacin until an up occurs and then discontinuing the drug. Eventually a down occurs, and you say the down has occurred because I stopped the drug. The down was probably going to occur anyway.

The defect in the trial is the drug is always given first and then the placebo given. The other defect is that Dr. Rothermich is not blind and when he saw the patients did not do well on a standard dose of indomethacin, he kept boosting the dose up to a level we would never use in practice, 400–500 milligrams. If you give any drug to supertherapeutic levels, you will get a response. I have no doubt that indomethacin is very effective in a dose of 400 or 500 milligrams a day but Rothermich himself said that 9 out of 10 of his patients who developed peptic ulcers were getting 200 milligrams daily.

Senator Scott. What drugs are used in treatment of the rheumatoid arthritis, Doctor?

Dr. O'Brien. A variety of drugs are used in the treatment of rheumatoid arthritis. The real question is what drugs are effective in the treatment of rheumatoid arthritis and there is considerable doubt that any drug will really do anything to stop the progression of this disease. Much of the treatment of rheumatoid arthritis is related to giving the patient an analgesic in relieving his pain, and bed rests and physiotherapy.

What drugs do anything except allay symptoms is very questionable and some authorities have questioned whether we should treat this disease. We may make the cure worse than the disease itself. Rheumatoid is not a potentially fatal disease. It lasts for 20 or 30 years and conservative therapy is indicated.

Senator Scott. Under the objective factors you have been discussing with regard to indomethacin, would aspirin be rated as a good drug for rheumatoid arthritis if it can be tolerated by the patient?

Dr. O'Brien. I would think that aspirin should be the standard therapy. Aspirin should be the first line of attack in rheumatoid arthritis.

Senator Scott. How accurately can you measure by objective means whether a patient feels better?

Dr. O'Brien. I would say that if a patient had a grip strength which indicated that he could not effectively grip and you gave a drug and his grip strength suddenly went up to 200 millimeters of mercury, this would indicate the patient had improved a great deal and I would say under these circumstances 99 percent of the patients would say they felt considerably better. I would grant there are some problems with subjective and objective evaluations. The important thing is that we not be misled by our own biases and thus, that when we do measure subjective responses that are variable, we compare that group which is on drugs to a group on some standard, either placebo or another drug, and make sure this is blind so that we do not mislead ourselves. The important thing is that the double-blind system is needed. We must keep the patient blind, too, because in using a new drug he may think this is a wonder drug and may report that he suddenly feels better. His improvement is not because the disease is better. It is because he is suddenly relieved. He thinks the doctor is going to get him better. The placebo effect is very important. If you have a headache 5 days in a row and think you have a brain tumor and the doctor examines you and tells you you are fine and gives you two aspirin, is the relief of anxiety due to the two aspirin? I think the reassurance on the part of the doctor plays a great part.

Senator SCOTT. Is Indocin used in the department of medicine at the University of Virginia?

Dr. O'BRIEN. It is rarely used.

Senator SCOTT. Is it not a fact that your department recently wrote the manufacturer for supplies of Indocin for patients who have benefitted from the drug?

Dr. O'BRIEN. If such a letter was written, it was not written by me. It may have been written by Dr. John Davis. I do not know.

Senator SCOTT. Would it not indicate maybe then that some of your associates hold different views from yours at the university?

Dr. O'BRIEN. This has not been apparent to me in discussing this with any of them. Of course, they are free to hold their own views.

Senator SCOTT. I used to teach there, too, and I found that some of my associates had different views than me.

Dr. O'BRIEN. I think Mr. Jefferson encouraged that at that particular university.

Senator SCOTT. Yes. I think Mr. Jefferson is the mentor whom I had in mind. But, it does suggest that, does it not, Doctor?

Dr. O'BRIEN. Yes.

Senator SCOTT. Have you personally conducted clinically controlled studies on indomethacin or is your testimony based on your attempt to recast the clinical studies of others into some formula?

Dr. O'BRIEN. I have had considerable experience using the drug, Senator.

Senator SCOTT. Mr. Chairman, may I ask that the article by Dr. Healey be included in the record at the end of the testimony?

Senator NELSON. The article will be included in the record.[1]

Dr. O'BRIEN. I will note that Dr. Healy's article relies on my article. I believe he cites this, does he not?

Senator SCOTT. He cites it but he does not necessarily agree with you throughout.

Dr. O'BRIEN. He certainly used it as a source.

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[1] See article beginning at p. 2847, infra.

(Correspondence from Dr. Healey to Dr. O'Brien follows:)

UNIVERSITY OF WASHINGTON,
Seattle, Wash., July 11, 1967.

WILLIAM M. O'BRIEN, M.D.,
University of Virginia, Department of Medicine,
Charlottesville, Va.

DEAR BILL: I am certain that you have much to do to get organized but I would be grateful if you could send me a preprint of your review of the indomethacin literature.

Many thanks,

L. A. HEALEY, M.D.

UNIVERSITY OF WASHINGTON,
Seattle, Wash., August 11, 1967.

WILLIAM M. O'BRIEN, M.D.,
Associate Professor of Preventive Medicine, University of Virginia, School of Medicine, Charlottesville, Va.

DEAR BILL: Many thanks for the draft. It represents a lot of work and the bibliography is most helpful. I agree with your comments and am delighted to see those studies reviewed critically.

One small quibble on page 19, line 2—phenomena are plural; one is a phenomenon.

Can you tell me when and where this will appear so that I may refer to it?

Sincerely,

L. A. HEALEY, M.D.,
Division of Arthritis.

Mr. GORDON. Mr. Chairman, there are a considerable number of articles on this subject and I ask that all of these articles be included in the record at an appropriate place.[1]

Dr. O'BRIEN. In retrospect, the early optimistic claims were based on vague experiments, which were scientifically unsound. The inadequacies of the early trials are painfully obvious. These include the well-known placebo effect, failure to consider the cyclical nature of rheumatoid arthritis, failure to account for spontaneous remission, and positive bias on the part of physicians testing the drug. These deficiencies are extensively documented in exhibit No. 1. The only scientifically sound method for drug testing is the controlled double-blind trial which eliminates both positive and negative bias and uses a comparison—either a placebo or a standard drug.

In January 1967, after the appearance of the four negative independent double-blind controlled studies, the company submitted six other positive double-blind controlled studies. Another Food and Drug Administration officer reviewed the records, and stated:

> Six new controlled studies are included, making a total of six controlled studies and 137 uncontrolled studies. It would seem, then, that any decision by us regarding efficacy, would rely heavily, if not completely, on the new studies, since the uncontrolled studies have already been disallowed. Review of the latter reveals they are totally inadequate and totally unallowable as evidence as efficacy of indomethacin for the new indications.
>
> Further critical consideration of these studies is contained in the bibliography, and let it suffice to say here that in general these studies are poorly conceived, poorly evaluated, and the efforts of the various investigators were poorly coordinated. When one turns to the controlled studies, it becomes disturbingly apparent that these are little better than the uncontrolled group. Three of the studies lack sufficient data to enable the reader to determine whether they were in fact controlled. Mention of the word placebo in an article does not confer on its control status. Good data showing placebo results is necessary to ensure the reader satisfaction that controls were indeed used.

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[1] See app. I beginning at p. 3001, infra.

In summary, 136 of 137 studies are grossly deficient in technique and incapable of standing up to the critical examination. It is unfortunate that the company and its investigators do not use more sophisticated investigative technique.

I can only agree with his analysis.

I would like to point out gross deficiencies in clinical trials are not limited to indomethacin. In fact, the clinical trials on indomethacin are better than with many other drugs. These deficiencies have repeatedly been pointed out, and my description of deficiencies in testing indomethacin is hardly anything new. I shall cite only two examples. In 1958 Foulds (J. Ment. Sci. 104:259) studied 72 British and American trials of drugs used in psychiatry, these publications covering the period 1951–56. Only 25 percent of controlled trials reported the drugs were useful, while 83 percent of uncontrolled trials were enthusiastic about the remedies.

Senator NELSON. Under what auspices were these trials conducted?

Dr. O'BRIEN. Foulds took every trial reported in certain psychiatric journals and looked at them to see whether they were adequately done.

Senator NELSON. My question was whether or not they were studies that were done under contract with the drug companies themselves?

Dr. O'BRIEN. I think most of them were done under contract with the drug companies but Foulds does not state. He does state, however, that "claims of success of treatment are closely associated with the absence of the means by which these claims can be scientifically substantiated."

In 1964 Mahon and Daniel (Canadian Medical Association Journal 90:565), studied 203 clinical trials published in Canada between 1956 and 1960. Only 5 percent were scientifically acceptable. This situation seems to be worsening in spite of Dr. Mainland's statement that clinical research is getting better, it would appear that at the time of marketing of indomethacin in 1965 and of mefenamic acid in 1967 the percentage of scientifically acceptable trials appears to have fallen to zero percent.

I feel that the Food and Drug Administration is all too willing to be convinced by the amount of data rather than the quality of data. The officials recognize the bias in each individual study, but feel they should accept 100 biased studies. There is absolutely no substitute for careful scientific work and one can never overcome bias in the design of studies by doing a great many such studies and repeatedly showing that biased studies always produced positive results. The officials do not seem to fully understand the necessity for double-blind controls; nor do they appreciate the necessity for either a placebo control or for a comparison with a standard established drug; nor do they insist on careful statistical analysis of results. The system encourages drug companies to do poor and sloppy testing. Why do a single careful trial, which might show a drug is useless, when the Food and Drug Administration is willing to accept many biased uncontrolled trials which are bound to show the drug is effective?

Mr. GORDON. It is your opinion, then, as I understand it, that before a drug is approved by the FDA, controlled double-blind studies should be conducted by objective sources. Is that correct?

Dr. O'BRIEN. Well, apparently it is not only my opinion but this is what the 1962 amendments said. They specifically required well-controlled studies. They do not say double blind, but certainly none of the 137 studies that were submitted were well controlled and 134 of these studies on rheumatoid arthritis did not have any controls at all. The other three were biased in favor of the drug.

Senator NELSON. Does the Food and Drug Administration have a set of established rules so far as the scientific testing is concerned, that have to be complied with in the NDA submission?

Dr. O'BRIEN. No, Senator Nelson. Any study can be submitted. In fact, some of the studies I saw were nothing more than testimonial letters where a doctor had written saying this was a great drug. These were based on giving the drug to as few as three people.

Senator NELSON. If it is correct that the only valid scientific method of evaluation, or at least a necessary part of the evaluation is a double-blind trial, why do you suppose the FDA does not automatically require it with every NDA?

Dr. O'BRIEN. I cannot answer that, Senator. I would think that there might be some justification in the first few trials of a drug to do uncontrolled trials. Unfortunately, Senator, what we see in medicine is that a few enthusiasts will do uncontrolled trials and report some drug is a panacea. The drug then comes into wide general use and then after many patients have been injured, someone will come along and do a careful study and show the drug is worthless. It will finally fall out of favor and then another drug comes along. I could cite dimethyl sulfoxide which was promoted solely on the basis of uncontrolled studies which lacked any scientific validity. I think we are seeing the same thing with cyclophosamide. This is a very dangerous drug being treated for rheumatoid arthritis and the trials are scientifically unacceptable. This drug causes bone marrow depression and may kill some patients. By the time someone gets around to doing a double-blind trial it may be too late. I think it is essential that one of the very first studies be a careful scientific trial, but, as in the history of indomethacin, the scientific inquires came fairly late in the game. They were published in 1967.

Senator NELSON. If it is so obviously necessary to have a reliable scientific report, it baffles me that it is not simply an automatic part of the procedure of the FDA to require it.

Dr. O'BRIEN. I cannot——

Senator SCOTT. It baffles you, too.

Dr. O'BRIEN. It baffles me, too. Yes.

Dr. MAINLAND. Might I interrupt for a moment because the term "double blind" could mislead people if it goes unqualified in the public press. In some trials it is quite impossible to do a double blind. From the point of view of Dr. O'Brien and myself this is obvious, but it might be overlooked when the term is emphasized, that if you cannot do it double blind then you have to do it by certain objective methods such as X-ray or blood tests or other devices whereby the bias can be stopped. The investigator, for example, in the steroid, the cortizone groups, can tell by looking at the patient's face whether he is on the drug or not. So, he could not possibly be in the situation of double blind.

Senator NELSON. Do I understand, however, that you would agree that in those cases where it was practicable to conduct a double-blind trial, it ought to be done?

Dr. MAINLAND. Absolutely. And there are ways that are not as widely recognized as they might be—namely, by getting other outside observers to make certain observations on the patients—one who will not know what the patient has. The physicians locally may have to know what the patient is receiving but as I see the future I rather think that probably will develop into quite a common system, whereby there will be certain people brought in to make special examinations and will not be informed as to which drug the patient has. It is quite feasible.

Senator NELSON. Thank you.

Dr. O'BRIEN. I suppose an example of the difficulty of doing double-blind trials is dimethyl sulfoxide which makes the patient smell like rotten eggs. I know of one investigator who attempted to use garlic dissolved in alcohol as a placebo.

Several trials on indomethacin were submitted by commercial drug testers. I feel the Food and Drug Administration should be very cautious in accepting information from professional drug-testing organizations. These institutions test drugs for a price and may not get further business unless the results are good. These commercial drug testers rarely produce unfavorable evaluations, and rarely report major toxic reactions.

II. THE TOXICITY OF INDOMETHACIN

When indomethacin was first released, physicians were led to believe it was relatively nontoxic—that it "extends the margin of safety in long-term arthritis disorders." This is from Merck ads which is exhibit No. 2. The initial studies of indomethacin indicated that it caused headache and that it occasionally caused gastric distress, but rarely produced peptic ulcer. Early in the history of the use of this drug, it was felt that many of the side effects were due to the hard pressed tablets which were used initially and that this problem had been alleviated by the introduction of capsules. As clinical experience since release of the drug has accumulated, it has become apparent that these initial reports were overly optimistic and that peptic ulcers were common. Not only did severe headaches occur but some patients became psychotic. The diarrhea that was noted in some patients was found to be due to actual organic lesions in the small bowel. Early animal studies reported that the drug actually increased resistance to infection. In humans it actually did the reverse and resulted in reactivation of old infection. In some children who received the drug overwhelming invasion of the body by bacteria, resulting in death, was reported. None of this was apparent when the drug was first released.

Surprisingly, most of the early uncontrolled trials reported far less toxicity than in the later controlled trials. Supposedly, observation of toxic reactions to a drug should be independent of the design of the testing procedure. In uncontrolled trials only 20 percent of patients were reported to have developed headaches while in the double-blind trials 47 percent were reported to have developed headaches. The uncontrolled trials stated only 7.7 percent of the patients developed abdominal pain and 2.1 percent developed peptic ulcers. In the controlled trials 2½ times more patients were stated to have experienced abdominal pain. 18.6 percent, yet only a fourth as many, 0.47 percent, developed peptic ulcers. This would indicate that patients in the double-blind trials were more carefully observed for signs of toxicity.

As a result, in the double-blind trials the drugs were discontinued more promptly, and fewer undesirable serious side effects, such as ulcers, occurred. Thus, the double-blind trial is not only scientifically more valid, but seems to be a far better way of detecting toxic reactions to drugs because of close, systematic observation required in this technique.

III. ADVERTISING OF INDOMETHACIN

Perhaps the worst aspect of clinical trials is not that they are bad, but how the shaky clinical evidence is promoted. Even though some trials are totally unacceptable to the Food and Drug Administration, they may be used in advertising claims after or even before a drug is approved. The Food and Drug Administration has already forced Merck to alter its ethical advertising of indomethacin several times.

Dr. Robert McCleery, of the Food and Drug Administration, has done an excellent job in regulating the worst abuses, but because of limited resources he has barely been able to scratch the surface. Dr. Desmond Gourley, chairman of the pharmacology department at the University of Virginia, devotes 5 percent of available teaching time in pharmacology to warning students about deceptive drug advertising. (Virginia Med. Mo. 93:459, 1966.) This year groups of four students were assigned 21 advertisements from recent publications, and instructed to find the pertinent literature in the library and grade the validity of claims according to criteria defined by Mahon and Daniel (Canad. Med. Assn. J. 90:565, 1964). These sophomore (these were not skilled practitioners) medical students found the claims made in the ads were unsubstantiated by sound experiments in 19 cases, 11 omitted unfavorable reports, and three misrepresented animal experiments. Of 170 references only 50 could be verified, and only three described sound experiments.

In the promotion of drugs, the committee should clearly distinguish between two types of medical journals—the legitimate scientific journals and "throw aways." The differences can be summarized in the table.

(The table referred to follows:)

	Throw aways	Legitimate journals
Example	Medical Tribune, Medical World News, and Current Medical Digest.	Clinical Pharmacology and Therapeutics, Arthritis and Rheumatism.
Economics sponsor	Usually advertising agencies	Nonprofit scientific societies.
Subscription	Sent without request	Only on request.
Cost to subscriber	Free	About $20 per year.
Circulation	200,000	2 to 5,000.
Advertising:		
Advertising per issue	50 to 150 pages	8 to 15 pages.
Location of advertising	Through text	Only before or after text.
Editorial policies:		
Scientific editing	Minimal	Careful, thorough.
Payment for articles	$300 and up	None.
Serious articles representing original contribution.	None	All.
"Promotional" articles	Frequent	None.

Senator NELSON. To go back to the previous paragraph, were these studies published any place?

Dr. O'BRIEN. These were just journal advertisements that were ripped out, given to the students. Some of them had references and the students were told, unlike the practitioner who reads them, go look up the references in the library. When the students tried to verify the references, they found many of them could not be found, or the references would be in obscure journals, or in the research files of some drug company.

Senator NELSON. Did anyone check the work of the students to determine whether or not it was accurate?

Dr. O'BRIEN. Yes. The students consulted with the faculty and the claims were evaluated in a session which lasted for half a day. Each team of four students presented their work and the results were discussed by the faculty.

Senator NELSON. Are the results of their study of these advertisements available?

Dr. O'BRIEN. I think the faculty will agree that in most cases the advertisements were unsubstantiated, and that the ads were deceptive. I think almost any objective scientist who went through the advertising in any journal would have no difficulty in detecting flaws in 90 percent of the advertising.

Senator NELSON. Thank you.

Dr. O'BRIEN. In the promotion of the drugs, I think the committee should clearly distinguish between two types of medical journals, the legitimate scientific journals and the throwaways. The difference can be summarized as in the above table.

These "throwaways" not only carry advertising but promote drugs by "news" articles which are not considered advertising. For example, the December 17, 1965, Medical World News carried the story "Indole Drug Keeps Its Promise," (exhibit No. 3). Strangely, the same physician writing in Consultant (a "throwaway" of Smith Kline & French), only 14 months later failed to even mention indomethacin in the treatment of rheumatoid arthritis (exhibit No. 4).

Even later, in February 1966, Current Medical Digest carried an article "Indomethacin: Welcome Breakthrough in Arthritis" (exhibit No. 5). This glowing report implied indomethacin was "not ulcerogenic,". and that other toxic effects were "irrelevant," even though numerous studies had already reported frequent serious toxic reactions. The drug was also promoted in a widely distributed symposium from Exerpta Medica.

The committee should understand that the "articles" in "throwaways" are not considered as advertisements by the Food and Drug Administration. These "throwaways," with their vast circulations and free subscriptions, are circumventing the usual rules restricting advertising, and crowding legitimate scientific journals off the desk of practitioners. The drug companies are gradually decreasing advertising support to legitimate journals, and pouring vast sums into the "throwaways." In my opinion, any journal with free subscription, sent to a physician without his request, which pays its contributors for nonoriginal contributions and is controlled by a profitmaking organization, should be considered advertising from cover to cover.

Senator NELSON. Are you saying that based upon the information submitted in the NDA, the FDA should not have approved this application?

Dr. O'BRIEN. I would think if they interpreted the law and the word control as I interpret it, they should not have accepted this application in 1965. That is my personal opinion.

Mr. GORDON. I would like to read the law to you. It says:

> The term substantial evidence means evidence consisting of adequate and well controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

Now, given the wording of this law, and this is directed to both of you, Dr. Mainland and Dr. O'Brien, what do we mean by substantial evidence?

Dr. O'BRIEN. Well, the law did define substantial evidence and made it clear that this was investigations by experts with adequate scientific training.

Mr. GORDON. In that particular drug; that is, if you are in the field of rheumatoid arthritis, I do not suppose you would get a doctor from the field of antibiotics.

Now, do you know if in any of these studies on indomethacin, being more specific for the moment, the investigators were, in most cases, experts in the field of rheumatoid arthritis?

Dr. O'BRIEN. I don't wish to get involved in passing on the qualifications of my colleagues. I think almost without exception the physicians who tested indomethacin were good physicians who were, for the most part, very well-qualified rheumatologists. The question is not whether they are good physicians and well-qualified rheumatologists but whether they are good scientists and properly evaluated the drug.

Many of these early studies which were submitted in the New Drug Applications were just physicians in practice giving the drug to their patients in a rather indiscriminate way, varying the dosages any way they wished. They were involved in a circular type of reasoning, and certainly not analyzing their data or seeing whether any of the changes which they saw in their patients were due to the natural fluctuations of this disease. This is a very variable disease. So, I would say these were not scientific experts.

I think perhaps in the first few studies this is justified, but to do all the studies this way is not. I would think you ought to have one or two studies like this and then start doing carefully controlled scientific experiments.

Dr. MAINLAND. I would like to make a comment on that. I agree with Dr. O'Brien. I would like to say somewhat as an outsider in this sense that I have not prescribed for patients, at least for a long, long time. My impression is, and this is not only in rheumatology but in the field of medicine generally, that a drug house sends a supply of drugs and the physician receives the drug and is asked to try it on a few patients. He does so and records his impression, and he may at the same time be doing controlled experiments. For example, one dermatologist whom I know who does this kind of thing in response to drug companies is doing very well controlled experiments in another area. They think—my impression is that they think—that this is a little bit of evidence that will just build up and give a general impression that there is something in this drug and then a good trial will be done.

Now, I think that is a very unfortunate sequence because the individual physician does not realize that he, and perhaps scores or hundreds of others, are being asked to do the same thing and then the manufacturer will present all this as a mass of a large number of patients. The individual physician may be actually scientific and yet feel that this is just a little bit of evidence. He knows it is uncontrolled, he says, "This is the impression I got from this treatment" and sends back the information to the drug house. So, it seems as if something should be done to stop that kind of thing.

I am rather against any kind of little haphazard preliminary testing because it ingrains in the minds even of physicians, it can tend to ingrain in their minds this impression: "This drug seems to have shown so much benefit. Can I now ethically take half my patients and give half of the patients that drug and keep the others from it?" I think it builds up an ethical conflict, this preliminary crude testing.

Dr. O'Brien. Is this not the genesis of the thalidomide catastrophe, that some quick preliminary things were done and then the drug started being indiscriminately used?

Mr. Gordon. That is correct. It was on an Investigational New Drug basis. Now, on the basis of your studies as well as the other controlled studies can you see any reason why a physician would prescribe indomethacin for rheumatoid arthritis?

Dr. O'Brien. I would say it has very limited use in rheumatoid arthritis. It might be worthwhile in patients who cannot tolerate aspirin and may be worth trying in some patients who do not respond to aspirin. Certainly, with patients with malignant rheumatoid arthritis, aspirin will not control the disease and neither will indomethacin. Because of the very severe toxicity and side reactions, I would say, any physician who uses indomethacin must watch his patients with extreme care. This is far more toxic than most drugs used in treating this disease. This situation, I do not think, would apply to acute gout. I think the drug is fairly effective in acute gout. Unfortunately, there have been no comparisons with standard therapy. I do not think any double-blind trials have been done. In ankylosing spondylitis Kinsella reported it relieved pain. Similarly in osteoarthritis in the hip there is no evidence of therapeutic effect. For these reasons I would think one would be very reluctant to try it. A simple analgesic would be better.

Senator Nelson. Is this drug a potential bone marrow depressant?

Dr. O'Brien. No. I think there have been some cases of leukopenia, but this is not one of the major side reactions of this drug. The major difficulties are with peptic ulcer.

Senator Nelson. I noticed a report in the New England Journal of Medicine reciting a case of aplastic anemia which came after the administration of indomethacin. I was just wondering if that were one of the side effects you are familiar with.

Dr. O'Brien. There are two types of side effects. Very common side effects and very rare. Diarrhea, headaches, peptic ulcer are very common. These other side effects are very rare and I think in all fairness to the drug, one would have to differentiate between this. I think that mental aberrations are extremely common. This drug is very dangerous in anyone who is using machinery or driving a car because it causes a woozy state and people may be accident prone. But many drugs will cause aplastic anemia and certainly indomethacin, I think, is probably far less dangerous in that respect than, say, phenylbutazone.

Mr. GORDON. On April 3, 1967, the Medical Tribune carried a statement by the Merck Co. concerning the studies done by the Cooperating Clinics Committee. Exhibit 1 submitted to the committee appears to be a point-by-point rebuttal of this statement. Now, did you send your rebuttal to the Medical Tribune?

Dr. O'BRIEN. When the Medical Tribune published Merck's statement that our study was invalid, Dr. Mainland urged me to complete this review. I did complete it and submitted it for publication in a legitimate scientific journal. This report was reviewed by Dr. Modell, the editor, and three referees. They sent it back to me, suggesting changes be made because they felt there were errors in parts of the text. Changes were made, the paper was published, and is documented with 108 references. I called this to the attention of the Medical Tribune and pointed out there was specifically a rebuttal of Merck's statement, but apparently they did not think it was newsworthy and did not mention it.

Mr. GORDON. The Merck Co. stated that it is difficult to do double-blind trials in arthritis and that it is unethical to use placebo controls. Do you agree with that statement?

Dr. O'BRIEN. Certainly not. In terms of double-blind trials, the technique certainly is more difficult because of the close systematic observation required, but is this not what we want in testing a new drug? We want the patient to be watched very closely to be sure there is not some toxic reaction. In one uncontrolled trial only 2 percent of the patients developed headaches on large doses of the drug. I doubt that this could be true, because on large doses the rate of headaches is around 50 percent. The controlled double-blind trial is difficult to do because it requires a great deal more work but it is a scientific way of assessing both the efficacy and the toxicity of the drug. As far as the placebo trials, if you do not think that any of the drugs you are using in a disease really help, I cannot see how you are going to hurt patients by giving them placebo, and I think this is the situation with rheumatoid arthritis.

If you had a disease where you were convinced that standard treatment did help, why not compare the new drug to the standard therapy? For instance, if you are interested in diuretics, and you were testing furosemide, a very potent diuretic, there is no possibility of withholding therapy. Why cannot you compare it with a standard diuretic, such as chlorthiazide? I think you can do a double-blind trial if you are willing to try. In the American Rheumatism trial we felt it was unethical to withdraw aspirin and we gave it and used it as a measure in the trial.

Mr. GORDON. Now, the Merck statement also says, "The study demonstrates fully that it is difficult to establish and successfully apply objective criteria that would permit measurement of the relative value of various drugs used in the management of rheumatoid arthritis."

What is your opinion on that question?

Dr. O'BRIEN. I think that is simply not true. The cooperating clinics of the American Rheumatism Association (Arthritis Rheum. 8:302, 1965) studied a series of 500 patients to determine what happens to the grip strength over a period of time, the time required to walk 25 feet, and the sedimentation rate, and so forth. Several trials have been done showing the observations. The late Dr. Bunim did some studies on the corticosteroids. These were all careful trials which demonstrated objective changes in joint function due to these drugs. Of course, the corticosteroids are very powerful antiarthritic agents. And the absence of showing these changes with indomethacin is probably not because they are impossible to show but because the drug you are using is not very powerful.

Mr. GORDON. The principal argument that Merck uses is that the drug has been studied by more than 300 clinical investigators, some of whom conducted controlled studies using placebo and several double-blind studies. They stated these are included in the New Drug Application. What is your opinion of these studies?

Dr. O'BRIEN. I share the opinion of the Food and Drug officer who reviewed these studies in 1967. He felt there was considerable doubt whether they were in fact double-blind controlled studies. He stated, and it is the fact, that he looked at these six and could not even tell from three of them whether they were controlled double-blind trials. Thus, in looking at these studies I do not think they are valid controlled blind trials. As far as the 300 investigators, as I pointed out in my testimony, there were indeed 300 investigators involved but a lot of them used the drug in less than 10 patients and experience with this small number of patients does not mean much.

Among the 300 investigators in that application there were many who were in the cooperating clinics. They used the drug briefly or early on, but later participated in, our controlled double-blind trials. I do not know the mathematics of saying 300 investigators used it and thought it was good. Many of the people who were in these preliminary trials later felt otherwise.

Senator NELSON. Dr. Mainland, did you have any comment to make about the Medical Research Council in England? I think that was mentioned previously.

Dr. MAINLAND. Yes. The analogy, I think, in this country would be something like the part of NIH that is concerned with the awarding of grants whereby the councils, panels, committees, study sections are outside investigators, most of them from universities. They are not government employees. That is the system of the Medical Research Council with regard to drug testing. Of course, they do not attempt to do a very large number of drugs. You could not build on the model of the Medical Research Council here except as a beginning, an idea, first of all, of independence, because the people who are investigating are employees of universities and other nongovernmental institutions and they are not members of drug houses or aided by drug houses. The system whereby they have set forth some of their trials is this, that the main council, having discussed with others and seeing that for a particular drug it is desirable that there shall be a systematic trial, develop what they call working parties. The working party is attached to a particular drug investigation and these working parties—some are members of the council and other similar people from other institutions—plan the scheme and they, going back very largely to their own institutions, allocate to the somewhat junior but not very junior people, the actual carrying through of the trial under the close supervision of the chief of the clinic.

In some instances, and that is true is our cooperating studies here—the clinic chief does some of the observing. So, in general, that is the picture of Medical Research Council with respect to drug tests.

Senator NELSON. Do they have a procedure similar to ours for making some sort of New Drug Applications which require approval at some stage by the Government?

Dr. MAINLAND. I do not know in detail what the system is. I am sorry. I had better not commit myself on impressions of what the English system is.

Senator NELSON. What is the exact name of your organization?

Dr. MAINLAND. Of this Rheumatism——

Senator NELSON. Yes.

Dr. MAINLAND. The Cooperating Clinics Committee of the American Rheumatism Association.

Senator NELSON. Is your committee financed exclusively by NIH?

Dr. MAINLAND. Yes.

Senator NELSON. When was this organization established?

Dr. MAINLAND. 1959. I think it was really in 1958 that we first received some money. I think we received first a few thousand from the Arthritis Foundation—but from 1959—that is our starting point.

Senator NELSON. What is the annual funding that you receive from the NIH?

Dr. MAINLAND. At present it is $135,000. At the time of indomethacin, that is because we received fairly recent new grants with more projects envisioned. At the time of indomethacin it was $100,000 a year.

Senator NELSON. Are there other similar committees dealing with other aspects of medicine funded by NIH?

Dr. MAINLAND. I am not sure of details.

Dr. O'BRIEN. I talked with some officials at the National Institute of Arthritis and Metabolic Diseases, National Institute of General Medicine Science, and they are funding several groups similar to ours but they do make a point that there are far more grants which are worthwhile which cannot be funded. They do not have enough money to fund all the things they would like to fund and they have earmarked specifically for clinical pharmacology only $3,500,000. This was earmarked by Congress.

In addition, the National Institutes of Health spends somewhere around $45 million a year on research in the field of drugs but much of this is basic biochemical work and not all of it is clinical testing. Certainly, their officials would indicate that there are not enough funds to fund all of the worthwhile investigations.

I think this is a very tragic aspect of clinical pharmacology. It is not a very attractive field for the young investigator. If you are working in some very exciting biochemical field which has great basic significance, it might be easier to get support. The young investigator who is not too well known may apply to the NIH and they may not be able to fund him because they have insufficient money even though his program is fairly good. He then has very few alternatives. He can try for something like a Burroughs Wellcome fellowship or support from the Pharmaceutical Manufacturers Association, but there is very, very little support here. What he eventually ends up doing is trying to do studies by getting support from drug companies on a quid pro quo basis for each little study. You cannot function with this type of erratic funding.

Another thing that is very unfortunate, is that if he turns in a bad report on a drug, he may lose his support. It is very unrealistic to expect the drug companies to support investigators who turn in bad reports on their drugs. So, once having turned in a bad report, the investigator probably is going to have trouble getting funding in the future.

Senator NELSON. I take it from your testimony that both of you think it is important that some method of objective independent evaluation be made of drugs, both prior to NDA approval and continuing afterwards; is that correct?

Dr. MAINLAND. Yes, that is quite correct.

Dr. O'BRIEN. I would concur and would just make the point that this 1962 legislation is the stepchild of a disaster (this was the thalidomide disaster) just as the 1938 act was a stepchild of a disaster (elixir of sulfanilamide). With more and more drugs being used, and more and more toxic drugs being used, and many more drugs being introduced in the pharmacopoeia, I think the era of great drug catastrophes is not past. We may have more in the future. I think this could occur unless careful testing is done. If we start this very uncontrolled testing and introduce a drug on the basis of uncontrolled trials and erratic observations, we may see other great catastrophes occurring.

Senator NELSON. Well, in your judgment about the quality of the testing done now for New Drug Applications, at least many of them, it is inevitable that at some stage we are going to have a catastrophe like thalidomide.

Dr. O'BRIEN. I would agree.

Dr. MAINLAND. Might I say a word or two about this matter of safety? Substantial evidence of safety. That presents another problem. Since I have the title statistician, I can give you a few figures.

My point is this. To obtain reliable figures, a drug must be very extensively used unless it really is a dangerous drug for many people. One has to see it used in many patients before perhaps a single case will emerge.

Let us imagine that some serious bad effect can occur in a drug. One hundred patients, we will say, do not show a single instance of bad effect. Now, if 1,000 similar patients were treated by the same drug in the same way, I would not be very much surprised if about 4 percent of those thousand developed a bad effect.

Why do I know that? Because I have been working with chance for years and decades and I know what kinds of things can happen by pure chance. You can get 100 patients quite free of this thing and then you may find that the next 1,000 will have—perhaps 4 percent in that thousand.

If there were no cases in 1,000 patients, I would be not very much surprised if several more thousands, perhaps 100,000, showed it about half of 1 percent. That is five per thousand. So, one has to visualize something that cannot be accomplished with regard to the rarer bad effects by any single drug trial. It is a matter of good recording of what happens when the drug has already gone into practice.

Now, another point that seems rather worthwhile looking at is that an acceptable risk for any drug depends partly on the disease, partly on the severity of the effect and partly on the patient. I think we might agree that a patient who is suffering greatly and nothing else has helped him, may be willing to take a 10-percent risk of something that is rather serious. What is necessary, therefore, is reliable information for the estimation of that risk so that you can say to a patient, "Well, there is 1 chance in 10 of this thing happening to you." He will say, "Oh, Doctor, I do not care. Let us try it."

Now, what I am trying to suggest is a system of reporting of occurrences and a knowledge of how many patients have been treated and to what extent. A patient who has received only a few doses without bad effects and then has dropped out, that patient should not count. Otherwise, it would be easy to have a very large denominator, a very large number of patients who had had the drug and nothing bad happened to them. But then, they have not had it in sufficient doses or sufficient length of time.

It is a big task. And the concluding point is that it should be, this task of collecting those reliable statistics should be, free from the influence of drug manufacturers.

Senator NELSON. I assume what you are saying is that there are simply some practical limitations on the information that can be gathered for purposes of estimating safety prior to the approval of a drug and its introduction into the marketplace for widespread use.

Dr. MAINLAND. That is right.

Senator NELSON. I want to thank both of you very much for your very valuable testimony. The committee appreciates it very much and it will be very useful to the record.

We will resume hearings at 10 o'clock tomorrow morning in this hearing room.

(Exhibits 1–5 submitted by Dr. O'Brien follow:)

EXHIBIT 1

INDOMETHACIN: A SURVEY OF CLINICAL TRIALS

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Indomethacin: A survey of clinical trials

Clinical trials of indomethacin in rheumatic diseases are reviewed. In treating rheumatoid arthritis, the good results observed in uncontrolled subjective and objective evaluations have not been confirmed in recent controlled double-blind trials. Failure to account for natural remission and cyclic variation in disease activity in uncontrolled trials probably explains these differences. There is no clear reason for preferring this drug over aspirin in treating rheumatoid arthritis. Indomethacin may be useful in treating other nonrheumatoid rheumatic diseases, but as yet few comparisons with standard therapies have been made. The drug has severe side effects and should be used with caution. Problems encountered in collecting information about this drug and its toxicity are discussed. The controlled double-blind trial appears to be the only feasible method for assessing both the efficacy and the toxicity of drugs used in treating rheumatoid arthritis.

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Indomethacin* was first reported as a useful anti-inflammatory drug for the treatment of rheumatoid arthritis (R.A.) in 1963.[65] Numerous reports confirmed its effectiveness. Recently, three carefully controlled double-blind trials[23, 69, 70] failed to show that indomethacin was superior to aspirin in treating R.A., and a fourth[19] could not distinguish between the effects of indomethacin and aspirin versus placebo and aspirin.

The results of these trials differed so greatly from previous reports that a reevaluation of all clinical trials of indomethacin was undertaken. In this perspective, the role and value of the controlled double-blind trial in evaluating drugs used in treating rheumatic diseases is appraised. The pharmacology of the drug is briefly reviewed. For convenience, the trials concerning R.A. are separated from trials in other rheumatic diseases. Toxic reactions to indomethacin are summarized, and the methods by which information on toxicity is collected are discussed.

Sources of information

Only publicly available, archival sources of information were used. An attempt was made to obtain all citations appearing in the *Index Medicus, Arthritis and Rheumatic Diseases Abstracts,* and *Current Contents.* A total of 132 citations were identified. Of these, 31 were discarded as either preliminary abstracts or duplicate publications. Eight foreign language publications

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*Trademarks: Indocin, Indocid, Indomee, and Amuno (Merck Sharp & Dohme).

could not be obtained, and this left 93 papers.

In this study these reports are classified in various categories. It is possible that another investigator might, in certain instances, make slightly different evaluations than the author. Therefore, all references are cited in the tables and the reader may repeat the experiments if he wishes.

Pharmacology

Although only a few basic pharmacologic studies of indomethacin have been published, a review of this information is helpful in interpreting clinical reports.

Interest in the anti-inflammatory effects of indomethacin was stimulated by the reports of abnormalities of tryptophane metabolism in R.A. In 1960, McMillan[57] reported an increase in the amounts of 3 hydroxyanthranilic acid in the urine of patients with R.A. Bett[4] and Spiera[89] confirmed this work and showed that after ingestion of trytophane a large increase in excretion of kynurenine (but not serotonin) metabolites occurred in patients with R.A., but only a moderate increase occurred in control patients.

Indomethacin was first synthesized by Shen and colleagues.[82] Hucker, Zacchei, and Cox[41] studied the physiologic disposition of indomethacin. The drug, having a half life of approximately 24 hours, was rapidly cleared from the plasma. It was excreted in the bile of dogs, monkeys, and guinea pigs. In monkeys and guinea pigs it was reabsorbed in the intestines and eliminated in the urine. However, in dogs the entire experimental dose was eliminated in the feces. Most of the excreted drug was present as the glucuronic acid conjugate. Harman and colleagues[37] found that most of the drug in animals is excreted unchanged or as its O-desmethyl and N-deschlorobenzoyl derivative. Man excretes indomethacin in the urine entirely as the glucuronide.

Studies of pharmacologic effects of the drug were carried out by Winter, Risley, and Nuss.[106] The potent anti-inflammatory effects of the drug were illustrated by the inhibition of granuloma formation due to cotton pellet implantation and edema due to the injection of carrageenin. In animals indomethacin was twice as potent as hydrocortisone, 35 times as potent as aspirin, and 25 to 100 times as potent as phenylbutazone. The drug was 10 times more potent than phenylbutazone in inhibiting fevers due to bacterial pyrogens. When indomethacin and corticosteroids were given together, their ability to inhibit granulomas was the summation of their effects alone. This suggested that the drug had a steroid-sparing effect.

The drug was effective in inhibiting granulomas when given either systemically or locally and was effective in animals which had undergone adrenalectomies, indicating that a pituitary adrenal mechanism was not involved in the anti-inflammatory effect. Boris and Stevenson[9] performed further tests on the effects of indomethacin on carrageenin-induced exudate formations. The drug was much more effective than either oxyphenylbutazone or phenylbutazone as an inhibiting agent. The exact site of action of the drug is unknown, but it does uncouple oxidative phosphorylation in cartilage and liver mitochondria.[105] The drug is about as effective as phenylbutazone in this respect. Walters and Willoughby[99] noted that indomethacin suppressed the erythema of tuberculin reaction in guinea pigs but did not effect the histological changes. They suggest that indomethacin acts by suppressing the lymph node permeability factor in delayed hypersensitivity reactions.

Ward and Cloud[103] used indomethacin in treating adjuvant-induced polyarthritis in rats. Both swelling at the injection site and generalized arthritis were suppressed when indomethacin was given at one half of the lethal dose (1 mg. per kilogram). In the same system, Fantini, Cattaneo, and Invernizzi[23] found only mild initial suppressive effects with no effect on the chronic polyarthritis. Rosenthale, Kassarich, and Schneider[75] found indomethacin to be about as effective as phenylbutazone in suppressing urate-induced synovitis in dogs.

Clinical trials of indomethacin in rheumatoid arthritis

The opinions concerning the value of indomethacin in the treatment of R.A. range from Norcross's[66] statement, "Indomethacin . . . appears to be more effective than any other anti-inflammatory drug for the long-term management of chronic arthritis with minimal toxicity to the patient," to the results of the controlled clinical trials[19, 23, 69, 70] which could not show that indomethacin had any advantage over aspirin.

All trials have been divided into three groups:

1. Papers which were based primarily on subjective evaluations. Several of these papers stated that objective measures of evaluation had been used, but the results

were actually based only on the subjective opinions of the patient or physician.

2. Studies which used some objective measures to evaluate the joint disease. These included such criteria as the number of painful, swollen, or tender joints, grip strength, ring sizes, timed walks, measurement of functional status, number of analgesic tablets consumed, and erythrocyte sedimentation rate.

3. Double-blind controlled clinical trials.

Table I compares subjective to objective uncontrolled studies. Those papers which reported improvement on a scale of excellent, good, fair, poor, and none were selected, and the percentage of excellent and good responses calculated. The subjective studies reported an average of 60 per cent good or excellent responses, while those studies using some objective evaluation reported only 25 per cent good or excellent responses.

Table II summarizes the results of the double-blind controlled trials. Some studies[16, 22, 33, 77, 84] which were partially controlled or partially blind are not included and are discussed later. The studies are divided into three groups based

Table I. *Improvement in rheumatoid arthritis in uncontrolled studies*

Type of study	*Number*	*Number of patients*	*% Good or excellent responses*	*References*
Primarily based on subjective evaluations	18	1,061	61.8	1, 5, 12. 16, 17. 20. 21, 22. 25, 49, 59, 64, 65, 67, 72, 77, 91, 94
Used some objective evaluations	6	310	25.1	11, 39, 48, 61, 92, 101

Table II. *Summary of double-blind controlled clinical trials in R.A.*

Comparison	*References*	*Cross-over*	*Aspirin ad libitum*	*Length of treatment (days)*	*Number of patients*			
					Total	*Drug*	*Placebo*	*Dropouts*
Placebo	102	+	+	28	29	29	29	0
	102	-	-	60	40	20	20	0
	101	+	Unknown	22	22	20	20	2
	19	-	+	84	136	56	53	27
Aspirin	70	+	-	14	42	38	38	4
	69	+	-	28	24	21	21	3
	23	+	-	28	30	30	30	0
Phenylbutazone (300 mg.)	68	+	Unknown	7	24	24	24	0
	39	+	Unknown	28	26	26	26	0

The plus sign = yes. The minus sign = no or absent. M.S. = morning stiffness. E.S.R. = erythrocyte sedimentation rate.

on comparison with inert placebo, aspirin, or phenylbutazone. In the crossover studies, the patient was his own control and received the drug first, then placebo, or vice versa. Consumption of aspirin was used as a measure of effectiveness in one trial.[19] No statement concerning control of aspirin intake is made in other trials.[39, 68, 101]

In comparisons with placebo, a significant difference ($p \leq 0.05$) in a few measures was demonstrated in the trial of Ward,[102] and a preference for indomethacin in the trial of Wanka and colleagues.[101] Although the trial of the Cooperating Clinics Committee of the American Rheumatism Association (ARA-CCC)[19] failed to show any difference between the indomethacin and aspirin group and the placebo and aspirin group, the indomethacin group did deteriorate more in terms of patient and physician opinion, but not in four objective measures, during the week after cessation of therapy.

In the three comparisons to aspirin,[23, 69, 70] the patients did not prefer indomethacin to aspirin. In one trial[70] grip strength increased during indomethacin therapy ($p = 0.05$). Other objective measures showed no difference in these three trials. The two studies comparing indomethacin to phenylbutazone showed no significant differences in objective measures. At a dose of 200 mg. per day of indomethacin, patients showed a slight preference for this compound[68]; but at a dose of 75 mg. per day indomethacin, the patients showed an overwhelming preference for phenylbutazone.[39]

Clinical trials of indomethacin in nonrheumatoid rheumatic diseases

The trials of indomethacin with other rheumatic diseases in which the number of excellent or good results were given appears in Table III. With a few exceptions cited later in this paper, the individual reports are subjective, brief, and involve small numbers.

Ankylosing spondylitis. About 70 per

Indomethacin dosage (mg.)	*Patient preference*		*Differences*	
	Indomethacin	*Comparison*	*Significant ($p \leqslant 0.05$)*	*Nonsignificant*
150-200			M.S., tenderness	Pain, swelling, grip
50-200			Pain, swelling, tenderness, grip, patient's and physician's evaluation	M.S., ring size
200-300	17	4		
50-200				Grip, inflamed joints, M.S., walk time, E.S.R., functional status, physician's and patient's evaluation
50-100	13	21	Grip	Ring size
50-100	7	7		E.S.R., grip, inflamed joints
50-125	13	13		Inflamed joints, analgesic tablets, M.S., grip, E.S.R., fatigue
200	10	7		Grip
75	1	15		Pain, M.S., grip, ring size

Table III. *Indomethacin therapy in other rheumatic diseases*

Disease	*Number of patients*	*% Good or excellent results*	*References*
Ankylosing spondylitis	185	71.3	5, 12, 20, 25, 47, 48, 59, 65, 68, 74, 77, 80, 94
Acute gout arthritis	175	83.7	3, 7, 12, 20, 25, 26, 32, 48, 49, 59, 64, 65, 68, 74, 77, 80, 87, 94, 101, 104
Osteoarthrosis	382	72.5	12, 20, 39, 48, 50, 64, 65, 71, 77, 91, 92, 94
Psoriatic arthritis	58	53.4	12, 20, 48, 59

cent of the patients had good or excellent responses. Michotte and Wauters[61] noted that patients with ankylosing spondylitis had prompt relapses when given placebo after indomethacin treatment. Hart and Boardman[39] compared indomethacin to phenylbutazone in 32 patients; 19 preferred indomethacin and 9, phenylbutazone. Several investigators commented that the best therapeutic results with indomethacin were obtained in the treatment of ankylosing spondylitis.[42, 80, 86]

Gout. About 80 per cent of the cases of acute gout responded. Relief occurred within a few hours in some cases, within 24 hours in most.[7, 26, 87]

Osteoarthrosis. The drug was reported effective as an analgesic in about 72 per cent of the cases. In trials treating the pain of osteoarthrosis of the hip, Wanka and Dixon[100] found a preference for indomethacin over placebo in 14 of 18 patients, while Zachariae[108] reported that 11 patients preferred 75 mg. of indomethacin, 7 preferred 300 mg. of phenylbutazone, and 1 preferred placebo. Michotte, Van Bogaert, and Wauters[60] found indomethacin gave relief of chronic hip pain but did not prevent radiographic progression of the disease.

Psoriatic arthritis. Joint symptoms responded in about 50 per cent of the cases. The drug had no effect on the skin lesions.

Rheumatic fever. Vignau and associates[97] reported a trial with 51 cases of acute rheumatic fever. Of these, 28 were treated with indomethacin and 23 with aspirin. No significant differences were noted between the two groups in terms of fever, sedimentation rate, electrocardiographic monitoring of the P-R interval, and the incidence of valvular heart disease 13 to 16 months after the acute attack.

Other rheumatic diseases. Indomethacin has been used in a variety of the less common rheumatic diseases. Most reports described a few cases followed for brief periods.

Reiter's syndrome. Six out of 8 responded.[48, 74]

Juvenile R.A. Twelve out of 13 children improved.[3, 74, 91]

Periarteritis nodosa. A steroid-sparing effect was noted in three cases, but no comment was made on improvement of the underlying disease condition.[3]

Polymyalgia rheumatica. Two reports stated that indomethacin was of little value,[68, 101] while another noted improvement.[53]

Palindromic rheumatism. Golding[34] reported that it relieved pain and swelling and stiffness in a case resistant to phenylbutazone.

Polymyositis. Three cases improved.[3]

Toxicity

Even during brief trials, a large percentage of patients taking indomethacin experienced untoward symptoms. In fifteen studies which reported the prevalence of side effects, 35.6 per cent of patients had at least one undesirable reaction.[1, 5, 11, 25, 30, 39, 48, 50, 53, 59, 67, 68, 72, 80, 91] In fourteen studies which reported the number forced to discontinue therapy, 20 per cent of the patients could not tolerate indomethacin.[1, 5, 12, 20, 21, 48, 50, 58, 68, 71, 74, 77, 91, 101]

Gastrointestinal. A total of thirty-five papers reporting use in 2,487 patients discussed the prevalence of gastrointestinal side effects.[1, 3, 5, 11, 12, 16, 17, 19, 21, 22, 23, 25, 38, 48, 50, 52, 53, 55, 56, 58, 61, 64, 68, 69, 70, 72, 74, 77, 80, 84, 87, 91, 94, 101, 102] Twelve per cent of these patients had nausea, 3.2 per cent experienced severe abdominal pain, and 2.1 per cent developed peptic ulcers. In a total of 60 patients, peptic ulcers were demonstrated. Where the site of the ulcer was clearly indicated, 16 were gastric, 14 duodenal, and 2 ileal. At least 12 ulcers perforated, and 18 bled massively. Vecchio, Fontana, and Tavazzi[96] gave indomethacin by stomach tube to rats. Hyperemia, congestion, and hemorrhages were seen in the gastric mucosa, and the severity of the lesions was dose related.

Acute pancreatitis has been reported.[35] Severe abdominal pain has usually been ascribed to gastric irritation, and the possibility of pancreatitis was not investigated in most studies.

Diarrhea occurs with indomethacin in about 10 per cent of the patients.[20, 50, 72] It can be severe and may possibly be associated with lesions in the small bowel. Shack[81] has reported 2 patients with ileal ulcers, perforations, and pathologic changes resembling regional enteritis.

Hepatic involvement is rare. A few reports mention abnormalities in liver function tests,[11, 48] usually minimal elevations in BSP retention, alkaline phosphatase, and transaminase. One case of cholangiolitic hepatitis[29] and one fatality in a child caused by a combination of hepatic necrosis and cholestasis are recorded.[51] Stomatitis has been described in a few patients.[50]

Central nervous system. Severe frontal headache is seen in at least one quarter of the patients. Although usually mild, headache becomes intractable in some patients and forces discontinuation of the drug. Other changes occur in less than 10 per cent of the patients but are more severe. Patients often complain of feeling light-headed, giddy, silly, or drunk. They are accident prone while in this state. Severe depressions, psychoses,[10, 23, 25] hallucinations,[92] and suicide[74] have been reported. Vertigo and dizziness are frequent symptoms and occur in about 15 per cent of the patients. Somnolence and stupor are infrequent.

Resistance to infection. Several cases of severe neutropenia have been recorded.[5, 62, 78, 91] Studies in animals indicated that indomethacin did not lower resistance to infection and large doses actually increased the resistance to infection.[73] This does not appear to be true in the human being. Solomon[88] reported three cases in which indomethacin probably caused reactivation of old sepsis in the region of the hip joint. Leukopenia was not present. Jacobs[43] reported four deaths in children. Overwhelming sepsis was the apparent cause.

Allergic reactions. Dermatitis is rare. Minor rashes have been reported in about 25 patients.[1, 3, 23, 38, 50, 64, 69, 70, 92] Itching and urticaria may occur.[48] Vanselow and Smith[95] have reported acute asthma and others have mentioned air hunger[50] and cardiac asthma.[101]

Eyes. Visual symptoms were not noted in initial trials. Recently, Burns[14] carefully examined 12 patients and reported changes in 11. These included corneal opacities, visual field changes, and pallor of the optic disc.

Miscellaneous. Single instances of other untoward effects ranging from acute myocardial infarction to temporal arteritis[46] are recorded. These are probably fortuitous associations.

Factors affecting toxicity

Tablets versus capsules. The first supplies of indomethacin were hard-pressed tablets. Many of the early variable results and toxicity were attributed to erratic absorption and direct toxic effects on the stomach. Later, the form of the drug was changed to capsules. Investigators who worked with both capsules and tablets indicated that the capsules were considerably less toxic than the tablets. Coste and colleagues[20] were forced to discontinue therapy in 36 per cent of the patients receiving tablets, but only 2.5 per cent of the patients receiving capsules. Similarly, Hart and Boardman[39] reported side effects in 66.3 per cent of the patients receiving tablets and 36.6 per cent of those receiving capsules.

Nevertheless, recent papers leave little doubt that capsules themselves cause significant toxicity. The number of patients reported to have withdrawn from trials was 17.3 per cent in papers published in 1964,[1, 5, 58, 68, 101] 25.4 per cent in 1965,[12, 20, 21, 48, 91] and 18.4 per cent in 1966.[50, 71, 74, 77] Since the capsules were used in all the papers reported in 1966 and most reported in 1965, it is unlikely that any significant decrease in toxicity has occurred.

Dose and toxicity. Few patients appear to tolerate more than 100 mg. per day without severe side effects. At doses of 150 to 200 mg. per day, from 60 to 70 per cent of the patients have toxic effects.[8, 50, 78, 79] Rothermich[77] reported 9 out of 10 patients who developed ulcers were receiving 150 mg. or more daily.

Suppositories. To avoid gastrointestinal irritation, suppositories have been used. Holt and Hawkins[40] found that suppositories produced good blood levels. Caruso and colleagues,[15] however, reported irregular absorption. Holt and Hawkins[40] reported local irritation in only 3 out of 10 patients. Whitehouse and Hart[104] used suppositories in 9 patients with good results and Rothermich[76] reported good results in 5. However, Woolf[107] found that 21 out of 43 patients could not tolerate suppositories; systemic effects still occurred and the patients found them less effective than capsules.

Type of study and prevalence of toxicity. The method by which changes in the arthritis are evaluated should have nothing to do with the reporting of toxic symptoms. Yet of 210 patients in six controlled double-blind studies,[19, 23, 30, 68, 70, 102] 47.1 per cent had headache and 18.6 per cent had severe abdominal pain; while of 1,663 patients in eighteen uncontrolled studies,[1, 3, 5, 11, 12, 17, 20, 21, 25, 48, 50, 58, 59, 64, 72, 74, 76, 94] only 20.9 per cent had headache and only 7.7 per cent had abdominal pain. In controlled studies only 0.47 per cent of the patients developed ulcers, while in uncontrolled studies 2.10 per cent of the patients developed ulcers.

Presumably, in the double-blind studies the patients were seen at regular intervals and carefully and specifically questioned about signs of intoxication. As a result, the drug may have been discontinued more promptly and fewer peptic ulcers developed.

Discussion

How can such differences between subjective studies, objective studies, and carefully controlled double-blind studies in R.A. exist? Several points concerning subjective evaluations and the use of controls may explain these differences. All of the points made here are well known and seem almost painfully obvious. But these phenomena were ignored in most clinical trials of indomethacin.

Subjective evaluations. Subjective evaluations primarily involve the use of patients' and physicians' opinions on improvement.

Patients. The chronically ill often are depressed and neglected. The sudden arrival of a "wonder drug" and new interest and concern by a physician may result in renewed hope and a sense of well-being, which often is interpreted as clinical improvement due to the drug. Identical response occurs with inert substances. Such reactions have been well described in 60 per cent of patients with chronic headache,[44] and 30 to 40 per cent of patients with postoperative pain.[2] These phenomena can be experimentally demonstrated in healthy medical students.[45] These patients are usually referred to as placebo reactors. Lasagna, Mosteller, von Felsinger, and Beecher[54] suggest that these effects are due not to imaginary complaints but to relief on the cortical level of the anxiety, fear, and despair that accompany pain and disease.

The phenomenon of placebo response is well known in R.A. Traut and Passarelli[93] treated R.A. patients with placebo tablets for periods of as long as 20 months. Good response was obtained in 50 per cent. When the patients failed to respond or ceased to benefit from oral therapy, placebo injections were given, and 64 per cent responded, some for as long as 30 months. Morison, Woodmansey, and Young[63] reported similar results and noted that the effect was more striking in initial placebo trials than in later ones. In the controlled trials on indomethacin, placebo response is evident. In the ARA-CCC trial[19] 48 per cent of the patients judged themselves improved on placebo therapy. In the week after cessation of placebo therapy, 25 per cent reported that their disease was worse.

Physicians. Doctors treating chronic diseases wish to help their suffering patients. New remedies are optimistically accepted and enthusiastically tried. The wry comment, "We must use new drugs quickly before they lose their power to heal," is true today. The doctors' enthusiasm and the seeming improvement in some patients may result in favorable reports. Drug companies may offer honoraria to physicians for testing drugs, and clinics may receive grants-in-aid. Subconscious desire to please a benefactor and fear of loss of further support may subtly bias evaluations in uncontrolled trials.

Objective studies. Studies using objective measures were much less enthusiastic but still reported that 25 per cent of the patients had good or excellent responses. Two factors which are independent of drug therapy may explain this improvement.

Failure to allow for the natural history of R.A. Short and Bauer[83] observed that 50 per cent of patients with R.A. showed definite improvement during prolonged observation. Duthie, Brown, and their associates[24] have made similar observations on large numbers of R.A. patients. At the first observation 26 per cent of the patients had very active disease and 10 per cent were inactive, while 9 years later 2.5 per cent were classed as very active and 24 per cent as inactive. In both series only aspirin and physical therapy were used as treatment. Thus, a significant number of patients have spontaneous remissions. In an uncontrolled study this improvement may be attributed to the therapeutic effect of a drug.

The tendency to start patients on therapy when they are deteriorating. R.A. is a disease characterized by cyclic fluctuations in disease activity. In the ARA-CCC 7 day variability study,[18] from 26 to 40 per cent of the patients showed deterioration in any one of four objective measures of disease activity, while 25 to 30 per cent showed improvement. Those with more severe disease activity showed a higher frequency of improvement than those with milder disease. Doctors rarely change medication when a patient is improving, and they feel forced to do something when the patient is getting worse. After a period of deterioration, a good percentage of patients will show improvement regardless of therapy. Natural remission and fluctuation in disease activity will make any antirheumatic drug appear effective in even an objective uncontrolled trial.

Controlled double-blind trials. Several studies which used comparison groups and placebos are not included in the list of double-blind controlled trials. Gaspardy and colleagues[33] used aspirin for 7 days before giving indomethacin for 6 weeks. Four other studies[16, 22, 77, 84] changed from drug to placebo in an arbitrary fashion and used placebo for varying lengths of time. Both Smyth[84] and Rothermich[77] introduced placebos when the patients had stabilized or shown maximum improvement on indomethacin. Smyth started indomethacin when placebo patients were getting worse. Since the disease is cyclic, if the patient has just gone through a period of improvement, starting a placebo will probably be followed by a period of deterioration; similarly, if a drug is started after a period of deterioration, improvement will probably occur independent of any drug effect. Katz, Pearson, and Kennedy[48] demonstrated this phenomenon and recognized the possible bias.

Only a small percentage of trials of indomethacin have been strictly controlled double-blind trials. Obviously the technique is more difficult. Fear that the use of a placebo might compromise the well-being of a test patient is unfounded. Several studies have shown that drugs do not alter the natural history of R.A. No series has claimed better end results than those obtained with simple, conservative therapy,[24, 83] and no decrease in joint destruction has been noted in treatment with even the most potent pharmacologic agents.[27] Naturally, a few months off therapy might make a patient uncomfortable, but it would not place him in any jeopardy nor would this discomfort be irreversible.

Are objective evaluations impossible? Payne[67] showed striking subjective response to indomethacin, but no objective changes. Potent anti-inflammatory drugs do produce measurable objective changes in R.A. Examples are the series of papers by Bunim and his co-workers[6, 13] studying corticosteroids in R.A. An example of a study of grip strength is the paper of Hajnal, Sharp, and Popert.[36] The failure to demonstrate objective differences in controlled trials of indomethacin seems to be due to a lack of potency of the drug rather than the impossibility of observing objective changes.

What therapy should be used in the contrast group? While contrast with placebo gives the clearest idea of the efficacy of the drug,[101, 102] contrasts with aspirin[23, 69, 70] are equally valid as a comparison with the standard form of therapy. An intermediate approach is a comparison against placebo, with the amount of aspirin consumed used as a measure of the efficacy of the test drug.[19] Interpretation of the results is confused unless aspirin intake is either constant or the number of aspirin tablets used is measured.

Seven years ago, the "XIII Rheumatism Review"[85] stated, "The natural history of rheumatoid arthritis, tending to intermittent exacerbations and variations with individual patients, has been discussed at length during the last ten years. . . . Despite these facts, many uncritical views prevail concerning the influence of certain clinical regimens or pharmacologic agents on the course and/or outcome of rheumatoid arthritis." In a disease as variable as R.A., the use of uncontrolled evaluation of a new drug seems totally unjustified. The occasional use of placebos and partially blind evaluation may actually bias studies even further. The controlled double-blind technique appears to be the most efficient method for investigating the merits of new treatments for R.A.

Toxicity. In some controlled trials[19, 23, 68, 69] identical inquiries were made in both the drug and contrast group. The difference is a good indication of the symptoms actually caused by the drug. Examples of the extreme variation in reporting of headache range from the uncontrolled trial of Morkel,[64] which reported 2 per cent headaches, to the controlled trials,[19, 23, 68, 69] which reported headache in 50 per cent of the drug patients and in 24 per cent of the contrast group. The controlled double-blind trial appears to be a more efficient and less biased method in assessing toxicity.

Smyth[84] states, "In the majority of patients the undesirable reactions occurred during the early weeks of therapy and either disappeared completely or became minor with continued drug therapy." Gastric ulceration, psychosis, and intercurrent infection all appear to be late toxic manifestations. No objective evidence that most toxic signs appear early or will decrease with the passing of time has been published.

Clinical use of indomethacin in R.A. The results of the double-blind trials[19, 23, 69, 70] indicate that indomethacin does not produce changes in R.A. which are distinguishable from those produced by aspirin. Double-blind trials of the drug's analgesic and anti-inflammatory effects in other situations reinforce these conclusions. Sunshine, Laska, Meisner, and Morgan[90] studied the analgesic effect of indomethacin in postoperative pain and reported that 50 mg. of indomethacin was equivalent to 600 mg. of aspirin. Vignau and associates[97] could not show that indomethacin has any advantage over aspirin in treating acute rheumatic fever.

The drug may be useful in patients who cannot tolerate aspirin, and some patients may do better with indomethacin. The drug obviously has many adverse effects and must be used with great caution.

Corticosteroid-sparing effects. Several authors were able to reduce drastically corticosteroid dosage in R.A. patients receiving both drugs,[3, 17, 38, 64, 65] in some instances completely discontinuing corticosteroids.[77, 84] Michotte and Wauters[61] give the only detailed description of attempts to withdraw steroids. In 12 cases, indomethacin capsules were given in doses of 225 mg. per day and prednisone was decreased 2.5 mg. every 24 hours. Within a week the condition of these patients had worsened, even though the indomethacin had been increased to 300 mg. per day. The authors felt that indomethacin could not be used as a corticosteroid-sparing drug.

Claims of corticosteroid-sparing must be interpreted with considerable caution since both drugs have gastrointestinal side effects. In the ARA-CCC trial,[19] an aspirin-sparing effect of indomethacin was noted. When nausea and abdominal pain occurred in patients receiving indomethacin, they generally took less aspirin. Thus, undesirable side effects rather than improvement appeared responsible. Until controlled studies are available, a true corticosteroid-sparing effect remains in doubt.

Long-term effects of indomethacin. Indomethacin may have long-term effects which are not apparent in brief controlled trials, but no evidence of cumulative effects of the drug or improvement after long periods of treatment has appeared.

Clinical use in other rheumatic diseases. Rothermich[77] states, "The high percentage of good and excellent results in nonrheumatoid benign rheumatic diseases would suggest that it is the drug of choice." While results in this group of diseases are very impressive, the reports represent subjective, uncontrolled observations. The natural histories of these diseases are even less well defined than that of R.A. One must assume that a certain amount of the improvement reported represents natural fluctuation in disease activity and placebo effects. Until controlled trials comparing indomethacin to established medications are published, it is unjustified to claim that indomethacin is a drug of choice in any of these conditions.

The drug is effective in acute gout in about 80 per cent of cases, but Wallace, Bernstein, and Diamond[98] report that 76 per cent of their cases responded to traditional colchicine therapy. Both drugs produce unpleasant side effects, so a careful comparison is needed. Controlled trials do show pain relief in osteoarthrosis, but the disease process is not affected, and indomethacin seems far more toxic than most analgesics. In rheumatic fever Vignau and colleagues[97] state, "Indomethacin appears to exert no effect on valvular heart disease and exhibits more side effects than aspirin. Its use in acute rheumatic fever should be reserved for rare patients other than those with peptic ulcers, who for some reason cannot accept salicylates."

No comparisons have been made in ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and so on. The drug should not be used in the arthritis of ulcerative colitis and regional enteritis, since it irritates the bowel.

Information on drugs. This review utilizes only literature available to any physician in any medical library. Much information on indomethacin exists as privileged, unpublished communications from the company to the Food and Drug Administration and it could be argued that this review is incomplete. For example, the first report on indomethacin, which is the most widely quoted citation on this drug and represents the largest clinical experience with the drug, is published solely as two very brief abstracts.[65, 66] Although unpublished information is used in supporting therapeutic claims and is accepted by the Food and Drug Administration, the clinical investigator cannot examine the evidence. He must rely on the judgments of the officials of the drug company and the Food and Drug Administration, and neither group appears to have the perspective or expert clinical knowledge to objectively analyze this information. It might better serve the public interest if only fully published, public data were allowed as evidence supporting therapeutic claims.

Methods for collecting information on the toxicity of drugs are very inefficient. Toxicity is not defined by any uniform criteria nor is it reported in a uniform way. The most standard way was to report the number of patients with a toxic symptom divided by the total number of patients in the trial. However, some trials report number of toxic symptoms per week of therapy[101] and others report number of toxic symptoms per episode of drug therapy.[84] Many papers enumerate individual toxic reactions but do not discuss the total number of patients having any one of many toxic reactions.

The Food and Drug Administration has set up a program for reporting toxic reactions in 150 teaching hospitals. In nine of the *Monthly Report of Adverse Reactions*[29] available to the author, seven reactions to indomethacin were reported. About 20 per cent of the patients in clinical trials had toxic symptoms severe enough to require discontinuation of the drug. If one assumes each of these had indomethacin for 50 days and takes into account Merck's statement that indomethacin has been used for more than 150,000,000 patient days, one might assume 600,000 reactions had occurred. Apparently only a tiny fraction of all reactions are reported to this program. Furthermore, neither the numerators nor denominators are given: not all reactions at an institution are reported, nor is the total number of patients receiving the drug given. Even though the system is inefficient, these reports should be made fully public by depositing them in medical libraries.

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EXHIBIT 2

From The American Journal of Medicine Vol. 41, No. 5 Nov. 1966

extends the margin of safety in long-term management of arthritic disorders

rheumatoid arthritis

"...the first non-corticosteroid agent which produced a predictable and measurable reduction in joint-swelling in most cases of active rheumatoid arthritis."

Hart, F. D., and Boardman, P. L.: Brit. Med. J. 2:965, Oct. 19, 1963.

ankylosing spondylitis

"Therapeutic results have been uniformly excellent or good in ankylosing spondylitis...."

Rothermich, N. O.: Arthritis Rheum. 7:340, June, 1964.

Indications: Chronic and acute rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, degenerative joint disease (osteoarthritis) of the hip, and gout.

Contraindications: Active peptic ulcer, gastritis, regional enteritis, or ulcerative colitis. Safety in pregnancy has not been established. Not recommended for pediatric age groups.

Warning: Patients who experience dizziness, lightheadedness, or feelings of detachment on INDOCIN should be cautioned against operating motor vehicles, machinery, climbing ladders, etc. Use cautiously in patients with psychiatric disturbances, epilepsy, or parkinsonism.

Precautions and Adverse Reactions: Most commonly, headache, dizziness, lightheadedness, G.I. disturbances. The C.N.S. effects are often transient and frequently disappear with continued treatment or reduced dosage. The severity of these effects may occasionally require cessation of therapy. G.I. effects may be minimized by giving the drug with food or with antacids or immediately after meals. Ulceration of the stomach, duodenum, or small intestine has been reported and, in a few instances, severe bleeding with perforation and death. Gastrointestinal bleeding with no obvious ulcer formation has also been noted; INDOCIN should be discontinued if G.I. bleeding occurs. As a result of G.I. bleeding, some patients may manifest anemia, and for this reason periodic hemoglobin determinations are recommended. Rare reports of effects not definitely known to be attributable to INDOCIN include bleeding from the sigmoid colon (either from a diverticulum or without a known previous pathologic condition), perforation of preexisting sigmoid lesions (diverticulum,

INDOCIN®
INDOMETHACIN

ANTI-INFLAMMATORY · ANALGESIC · ANTIPYRETIC

a new, highly effective nonsteroid anti-inflammatory agent

degenerative joint disease (osteoarthritis) of the hip

"I have had some 500 patients on indomethacin now for about three years. I find it an extremely helpful drug. I think there are certain areas where it will be without question the drug of choice. One of these is osteoarthritis of the hip."

Englund, D. W., in Nonsteroidal Anti-inflammatory Drug Therapy in Rheumatic Disease, New York, Excerpta Medica Foundation, 1965, p. 27.

gout

"Indomethacin is the drug of choice in acute gout...."

Hart, F. D., and Boardman, P. L.: Brit. Med. J. 2:965, Oct. 19, 1963.

carcinoma), and hematuria. In other rare cases, a diagnosis of gastritis has been made while the drug was being given. One patient developed ulcerative colitis, and another, regional ileitis, while receiving INDOCIN; when the drug was given to patients with preexisting ulcerative colitis, there was an increase in abdominal pain. Infrequently observed side effects may include drowsiness, tinnitus, mental confusion, depression and other psychic disturbances, blurred vision, stomatitis, pruritus, edema, and hypersensitivity reactions. Slight BUN elevation, usually transient, has been seen in some patients, although the preponderance of evidence indicates that INDOCIN does not adversely affect renal function, even in patients with preexisting renal disease. Nevertheless, renal function should be checked periodically in patients on long-term therapy. Leukopenia has been seen in a few patients. Transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, and thymol turbidity tests have been observed in some patients and, rarely, elevations of SGOT values; the relationship of these changes to the drug, if any, has not been established. As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

Before prescribing or administering, read product circular with package or available on request.

MSD MERCK SHARP & DOHME Division of Merck & Co., Inc., West Point, Pa.

where today's theory is tomorrow's therapy

EXHIBIT 3

[From Medical World News, Dec. 17, 1965]

INDOLE DRUG KEEPS ITS PROMISE

TESTS SHOW INDOMETHACIN TO BE STRIKINGLY EFFECTIVE DESPITE SOME DRAWBACKS

Almost three years of clinical trials have established indomethacin, an indole derivative, as the most promising antirheumatic agent since cortisone, a Denver investigator declares. The drug, which is unrelated to the adrenocorticosteroids, has proved strikingly effective against gouty arthritis and rheumatoid spondylitis, reports Dr. Charley J. Smyth of the University of Colorado. Its usefulness extends to patients with rheumatoid arthritis and osteoarthritis.

Dr. Smith points out that indomethacin (*Indocin*, Merck Sharp & Dohme) has certain unpleasant, though not serious, side effects. "In our study, the relative frequency of the five most commonly observed side effects during 1,128 weeks of indomethacin therapy on 46 patients with 90 drug trials was headaches, 48%; nausea, 38%; heartburn, 23%; vertigo, 19%; and vomiting, 10%."

When these symptoms did not appear or when they could be avoided by reducing the dose, indomethacin was found to have a very quick anti-inflammatory and analgesic action in cases with acute gouty arthritis. Marked reduction of pain was observed within two to four hours, while inflammation disappeared within three or four days. 'In a series of 35 acute episodes of gout, this drug was as effective as phenylbutazone or colchicine without their potential hazards." Dr. Smyth recommends an initial large dose, 100 mg to 200 mg, followed by 50-mg doses at two-hour intervals during the first day.

Further investigation, he says, will probably document the effectiveness of indomethacin combined with uricosuric agents for chronic gouty arthritis.

Dr. Smyth treated 30 patients with ankylosing or rheumatoid spondylitis. In most of those who had active disease without advanced bony or ligamentous calcifications, he observed striking and sustained clinical improvement. Back and neck pains decreased and disappeared, as did the associated muscle spasm. In these cases, he used a low initial daily dose of 25 mg or 50 mg for five to seven days. This total daily dose was then progressively increased by 25 mg each seven to 14 days until a maintenance dose of 100 mg to 150 mg was reached.

Only objective findings were recorded and no appraisal of the patient's subjective response to therapy was made. This study group comprised 55 patients with active rheumatoid arthritis at stages I to III to whom indomethacin, and a placebo were given alternately. Following this pattern for 32 months, Dr. Smyth concludes that indomethacin does exert an anti-inflammatory and pain-relieving effect, but may require two to four months to elicit maximum therapeutic response.

Gradual withdrawal achieved

The steroid-sparing effect of indomethacin was confirmed. In 20 out of 30 patients receiving adrenocorticosteroids, the amount of steroid could be decreased by stages after they had started taking indomethacin. In 16 patients, the steroids could be withdrawn completely, and in four, the total daily dose of steroid was reduced by 50% or more.

Dr. Smyth considers indomethacin's side effects a factor that should always be taken into consideration. The drug should be prescribed cautiously for patients with a history of peptic ulcer or gastritis. Its use should be discontinued if gastrointestinal bleeding occurs. Indomethacin suppositories might help solve some of the gastrointestinal problems. There have been a number of reports detailing the satisfactory absorption of the drug from the rectum. There were no gastric complications or disturbances in 40 patients for whom oral therapy was contraindicated or whose total daily dosage was increased above 150 mg.

Infrequently, patients complained of drowsiness, mental confusion, depression, and a feeling of detachment or a sensation of "floating in the air." Since extensive laboratory studies did not detect any toxic systemic effects induced by this drug, and the negative effects described by Dr. Smyth disappear as soon as the medication is reduced or stopped, he suggests that all rheumatic patients be started with small daily doses, slowly increased to the maintenance level.

EXHIBIT 4

[From Consultant, April 1967]

(By Charley J. Smyth, M.D., University of Colorado)

Charley J. Smyth is Associate Professor of Medicine and Chief of the Arthritis Division of the University of Colorado School of Medicine. He is also Associate Editor of the journal Arthritis and Rheumatic Diseases; a section editor of Hollander's text Arthritis (Lea & Febiger); and the author of 75 scientific articles on arthritis and related diseases. Doctor Smyth is a Fellow of the American College of Physicians and a member of the American Rheumatism Association.

TREATING RHEUMATOID ARTHRITIS: WHAT'S MOST APT TO SUCCEED?

Time tests many things, and certainly the efficacy of various medical, therapies. Some that at first appear highly effective turn out to be unreliable or too risky; others that at first appear to be too risky turn out to be the best in the long run. So it has happened with various therapies for rheumatoid arthritis.

Certain ones are indisputably effective: rest, relief of pain with salicylates, planned exercise, and a well-balanced diet. Others have only partial chances of success against rheumatoid arthritis.

STEROIDS: VALUABLE FOR SHORT-TERM TREATMENT

Steroids are most valuable when given for a short time and for a special reason: to enable a patient to carry out a painful exercise program; to permit him to complete a necessary job; or to suppress articular inflammation and pain while starting therapy with a slow-acting drug such as gold, indomethacin, or one of the antimalarials.

To be effective, steroids must be taken *daily*. If taken on alternate days, they will not reliably suppress inflammation. Steroids should also be given in the *lowest effective dose*, hopefully to avoid their well-known complications such as peptic ulcers, Cushing's syndrome, infections, osteoporosis, and vasculitis. The total daily dose should never exceed 10 mg. of prednisone or its equivalent. And the daily dosage should be reduced gradually by 1 mg., every three to five days if possible.

Since cortisone was discovered, researchers have continuously sought more potent and less toxic anti-inflammatory compounds. However, all of the new steroids seems to have the same potential hazards and few offer any advantages over prednisone or prednisolone. In fact, the increased potency of some has proved to be a decided disadvantage—fine dosage adjustments are impossible.

PHENYLBUTAZONE: SAFER THAN ONCE THOUGHT

We used to fear bone-marrow suppression from phenylbutazone. However, after many years of widespread use, it is now considered a valuable anti-inflammatory agent with a small incidmence of serious side effects. Many patients with rheumatoid arthritis tolerate and respond to phenylbutazone better than any other drug. It is often well worth using, provided, of course, that the patient is given the necessary follow-up examinations and periodic blood tests.

The analogue of phenylbutazone, oxyphenbutazone, has not proven to be superior. It requires larger doses, milligram for milligram, to produce equivalent antirheumatic effects; moreover, these larger doses produce about the same toxic effects as phenylbutazone does.

THE ANTIMALARIALS: NOW APPEAR RISKY

Recent reports of irreversible retinal vasculitis leading to blindness have dampened enthusiasm for chloroquine and hydroxychloroquine in rheumatoid arthritis. If an antimalarial must be used, hydroxychloroquine is the safer of the two. Nevertheless, every patient receiving it should be given a thorough retinal examination at least every six months.

GOLD: STILL THE MOST EFFECTIVE

Gold therapy has not had glittering success in rheumatoid arthritis. Yet it consistently gets a high rating from physicians who use it. Many believe that gold, given under rigid supervision, may be the only thing that changes the course of the disease.

The absolute necessity in using gold is to do blood counts and urine tests frequently—preferably before each dose—and to stop it if there is any sign of hematopoietic or renal toxicity. It should also be stopped if the patient reports or shows evidence of pruitus, dermatitis, or stomatitis. Gold must be used with caution but its advantages outweigh its potential disadvantages, particularly in rheumatoid patients with peptic ulcer.

Exhibit 5

[From Current Medical Digest, February 1966]

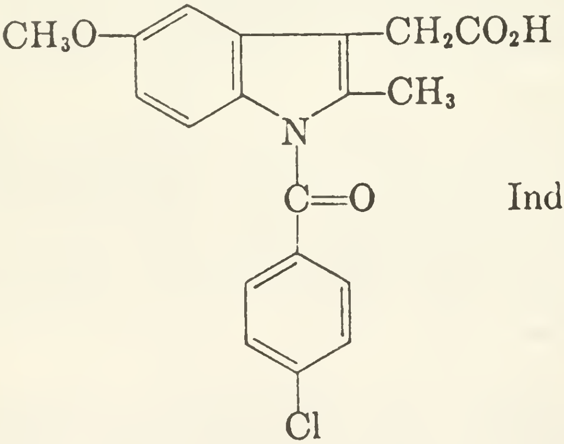
Indomethacin: Welcome Breakthrough in Arthritis

(By John C. Krantz, Jr., Ph.D.)

John C. Krantz, Jr., Ph.D., is co-author of *The Pharmacologic Principles of Medical Practice* and Professor Emeritus of Pharmacology, University of Maryland School of Medicine.

Oil of wintergreen and sodium salicylate were used in the treatment of rheumatic pain during the 19th century. Felix Hoffman introduced aspirin for the treatment of rheumatoid arthritis at the dawn of the present century. For nearly 7 decades it has remained one of the drugs of choice in the treatment of arthritides. We waited almost a half century for the observation of Philip S. Hench of the Mayo Clinic for the introduction of the corticosteroids in arthritis. In his first paper Hench states, "Usually, the fibrostic component (muscular and articular stiffness) began to diminish first, often within the first 48 hours . . . and was often markedly or completely relieved within a few days." The use of the steroids has been salutary, but not without serious side effects in many cases.

And now another break through "indomethacin" (Indocin—Merck Sharpe & Dohme) has occurred. Indomethacin is a 3-indolyl acid derivative of the following chemical composition:



Indomethacin

(1-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid)

Whitehouse classifies antirheumatic drugs according to their *in vitro* activity:

1. Those which primarily inhibit oxidation (by interfering with an enzyme(s) in the electron transport chain) and have slow, irreversible activity of such compounds that may, in part, account for the relatively troublesome side reactions noted *in vivo*.
2. Those which primarily uncouple oxidative phosphorylation (*i.e.*, selectively inhibit the biogenesis of adenosine triphosphate (ATP) without inhibiting oxidative metabolism and cellular respiration) and have rapid and reversible action.

Indomethacin, salicylates, flufenamic acid, phenylbutazone, and gold-sodium thiosulfate were shown to uncouple oxidative phosphrylation in rat liver mitochondria and also in a connective tissue (cartilage). Both the incorporation of inorganic phosphate-P into organic phosphates and the ATP-dependent biosynthesis of mucopolysaccharide sulfate were selectively inhibited without significantly affecting the oxidation of glucose-^{14}C and octanoate-^{14}C by the cartilage tissue.

Indomethacin and phenylbutazone were approximately equipotent as uncouplers of oxidative phosphorylation in rat liver mitochondria. Indomethacin was slightly more active than phenylbutazone in inhibiting cartilage metabolism.

Indomethacin has been shown to evoke analgesia, antipyretic, and anti-inflammatory action.

There are many clinical reports indicating that this new non-steroidal agent is a competent competitive drug with aspirin and the steroids in the treatment of the arthritides. For example, W. D. Paul, distinguished rheumatologist of the University of Iowa states:

"In summary, continued clinical experience has shown that, when used properly, indomethacin, a new non-steroidal, antirheumatic agent, is a safe and effective drug in the management of rheumatoid arthritis. Indomethacin provides good anti-inflammatory, analgesic, and, in some cases, antipyretic effect. In addition to these therapeutic activities, indomethacin can also often provide a steroid-sparing effect. The user of indomethacin should remember that this agent is not to be considered rapid-acting, and, therefore, an adequate trial at *low* dosage should be permitted before considering a lack of patient response as an indication of product failure. Also, indomethacin should not be used in treating self-limited joint pain.

"Irrelevant effects seen with the use of indomethacin have been mild, usually dose related, and rarely require cessation of the medication. With the use of capsules and careful regulation of dosage, 3 out of every 4 patients have had no irrelevant effects. Headache and dizziness have been the most frequent symptoms, but these can usually be easily controlled. Epigastric distress has been the most common of the gastrointestinal complaints but this, too, can usually be handled easily, often by simply insisting that the drug be taken with meals. It is the belief of the Iowa group that indomethacin is not ulcerogenic.

"When used wisely, indomethacin is an exciting and potential ally in the physicians' war against rheumatoid arthritis, the Nation's leading crippler" (*Medical Information Bulletin 6:* No. 7 and 8, Aug.–Sept. 1965).

(The article by Dr. Healey, previously referred to, follows:)

[From Bulletin on the Rheumatic Diseases, vol. 18, No. 4, December 1967, pp. 483–486]

AN APPRAISAL OF INDOMETHACIN*

The introduction of indomethacin (Indocin, Merck, Sharp and Dohme) has aroused more interest, controversy and discussion than any anti-rheumatic drug since the corticosteroids. Conflicting reports of its efficacy, potency and toxicity have appeared in scientific journals and in the medical and lay press. It was widely used as an experimental drug even before it became available for general prescription use in 1965. Since that time, sales figures attest to the popularity.

This review is an attempt to place it in perspective as an anti-rheumatic agent based on the experience accumulated since its introduction. Its chemistry, pharmacology and metabolism will be considered as they relate to clinical activity. The range and potency of its therapeutic effect are discussed together with its demonstrated limitations and toxicity.

This is not a literature survey. A comprehensive and critical review of the clinical studies with indomethacin has been compiled by O'Brien.[1] The discussion that follows owes much to that paper. It is strongly recommended not only as a complete bibliography of indomethacin but also because the method of evaluating published reports which O'Brien describes is useful in weighing claims for any therapy.

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*From the Division of Arthritis, Department of Medicine, University of Washington.

[1] O'Brien, W. M.: Clin. Pharmacol. & Therap. In press.

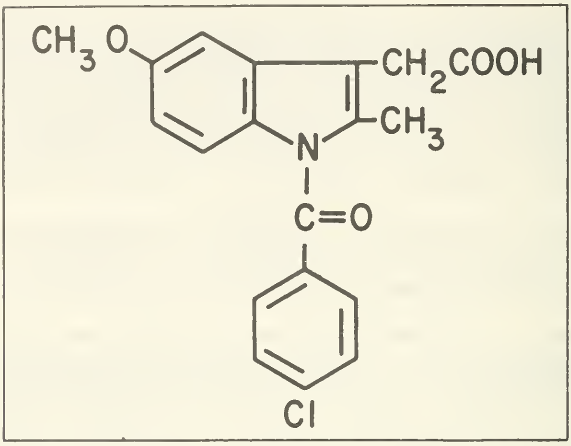

Fig. 1.—Chemical Structure of Indomethacin.

STRUCTURE AND MODE OF ACTION

Indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) is an indole acetic acid derivative, a weak organic acid. Its structure is shown in Fig. 1. It is *not* a steroid derivative. According to the manufacturer, the potential role of 5-hydroxytryptamine (seratonin) in inflammation prompted a systematic examination of more than 300 indole acetic acid compounds, from which indomethacin was chosen.

Its anti-inflammatory activity has been demonstrated in two standard laboratory assays, the inhibition of granuloma formed by subcutaneous cotton pellets and the inhibition of carrageenin-induced edema. By these accepted measures, indomethacin is very effective, its potency exceeding equivalent doses of aspirin, phenylbutazone and hydrocortisone. In laboratory animals, antipyretic activity could also be demonstrated. The mechanism of the anti-inflammatory activity is unknown, which is also true of the other drugs in current use. All of them have been demonstrated to uncouple oxidative phosphorylation, but it is not certain that this is the basis for their influence on inflammation.

There are marked species differences in the metabolism and route of excretion of indomethacin. In man the drug is rapidly absorbed and excreted. Following an oral dose, peak blood levels are obtained within two hours and the biologic half life is less than 24 hours. Between 90% and 95% of indomethacin in the circulation is bound to plasma proteins, mostly to albumin. The bound compound has been identified as unaltered indomethacin, not a metabolite. Approximately two-thirds of an administered dose is excreted by the kidney and the remainder appears in the feces. When isolated from urine, the indomethacin has all been converted to the glucuronide; no glucuronide is present in the circulation. The clearance of indomethacin exceeds that of inulin (or other measure of the glomerular filtration rate), even without correction for the 90% bound to protein, indicating efficient secretion by the renal tubule cells. These observations indicate that indomethacin, bound to protein, is not filtered; it is conjugated to the glucuronide in the kidney and is avidly secreted by the renal tubular cells.

The protein binding and the secretion as a weak organic acid indicate two possible loci where the interaction of indomethacin with other drugs might have clinical significance. Competition for protein binding may release more free—hence active—indomethacin into the circulation. For example, such an action has been demonstrated with coumadin, where phenylbutazone displaces coumadin from the protein bond so that a proportionate dose exerts a greater anticoagulating effect. Similar competition for protein binding sites has been postulated for phenylbutazone and salicylate as well as for other compounds.

The second possible site of interaction is the renal tubule where the weak organic acids are secreted by a common mechanism. Perhaps the classic example of this effect is the interference of probenecid with the excretion of penicillin. At one time this was used to increase the blood levels of penicillin obtainable with a given dose of the drug. We have observed such inhibitory action of probenecid on the excretion of indomethacin. While this effect is definite, it is not sufficient to delay excretion and increase blood levels to clinically significant ranges. It is worth noting that indomethacin does not increase or decrease the renal excretion of uric acid. The possible interaction of indomethacin with other drugs, particularly salicylate, has not been tested.

CLINICAL USES OF INDOMETHACIN

Under Food and Drug Administration regulations, the recommended uses of indomethacin are limited to specific conditions: rheumatoid arthritis, ankylosing spondylitis, gout and degenerative joint disease of the hip. Its use in these four diseases will be considered.

Rheumatoid arthritis

The most important and most controversial aspect of indomethacin lies in its use in rheumatoid arthritis. This is a situation in which an effective medicine is badly needed because of the number of patients affected, the disability produced and the lack of other completely satisfactory therapy. O'Brien has divided the reports on the efficacy of indomethacin in rheumatoid arthritis into three groups as follows:

1. Uncontrolled studies, subjective response only.
2. Uncontrolled studies, some objective measurements of response; such as grip strength, fall in sedimentation rate or change in joint appearance.
3. Controlled studies.

The point has been made before that it is extremely difficult to judge the efficacy of a medication by subjective responses and uncontrolled studies. However, as Bradford Hill said in his Heberden Oration, "Since apparently no one was listening, it can safely be made again."[2] In a chronic disease such as rheumatoid arthritis, which is marked by spontaneous remissions and exacerbations, where both the patients and physicians naturally are hoping for improvement, the subjective impression of the efficacy of any drug is inadequate to judge its value. This point is well illustrated in O'Brien's two groupings. The percentage of "good" responses in the totally subjective evaluations was 62%. When any objective measures at all were attempted, this percentage of "good" responses fell to 25%. These studies should be compared with the observations of Short and Bauer who showed that 50% of patients with rheumatoid arthritis will improve with the most conservative treatment.[3]

It is apparent that more reliable information on effectiveness of indomethacin can be obtained from the third group, the controlled studies. These are of three types, all double blind: comparison with a placebo, crossover with a placebo, or crossover with another drug, either aspirin or phenylbutazone. The daily dose of indomethacin ranged, in general, from 50 to 200 mgm.

In considering those eight studies in which indomethacin has been tested in a controlled double blind situation, the following observations can be made. 1) In no instance was it possible to demonstrate objective evidence of anti-inflammatory action. 2) When used in a crossover with placebo, more patients preferred indomethacin (17 to 4). 3) When used in crossover studies with phenylbutazone or aspirin, there was no convincing difference in patient preference. In the largest double blind controlled study, indomethacin was compared with the placebo without crossover.[4] Both groups were allowed aspirin *ad lib*. There was no demonstrable difference in objective changes or subjective response between the two groups. The drug-treated patients however did report a decrease in their aspirin consumption significantly greater than that of the patients taking placebo.

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[2] Bradford Hill, A. : Ann. Rheum. Dis. *25* : 107, 1966.

[3] Short, C. L. and Bauer, W. : New Eng. J. Med. *238* : 142–148, 1948.

[4] Report of the Cooperating Clinics Committee of the A.R.A. Clin. Pharmacol. & Therap. *8* : 11–37, 1967.

From all of these observations, certain conclusions can be drawn. First, indomethacin possesses some anti-inflammatory effect; it is clearly preferable to an inert placebo. The fact that few if any objective changes could be demonstrated with its use does not mean that it is inert. The experience with other anti-inflammatory drugs of limited nature such as aspirin, phenylbutazone and chloroquin has been the same. Therefore, and second, indomethacin is of limited effectiveness as an antirheumatic drug. It does not approach the potency of the corticosteroids as shown by the definite change in objective measures in the study of prednisone. Rather, and third, indomethacin closely resembles aspirin in its anti-rheumatic potency. This is true in crossover studies where there was little difference between the two in patient preference. This may also be inferred from the Cooperating Clinics study where there was no demonstrable difference between indomethacin and placebo groups when both were allowed aspirin *ad lib.*

This result is best explained by postulating that indomethacin replaced some of the daily aspirin dose in the patients on drug and this effect was matched by a larger dose of aspirin in the placebo group. (It is, of course, also theoretically possible that aspirin may have interfered with the action of indomethacin by some mechanism similar to those described previously.)

Despite these controlled trails, many physicians have the impression that indomethacin benefits some patients with rheumatoid arthritis. This implies that there may be a certain kind of rheumatoid arthritis, a sub-group, which is controlled by this drug (usually in a daily dose of 75 to 100 mgm) but which is not identified when such patients are included in a general population in a drug trial. This may be true; the hypothesis is susceptible of proof but it has not been tested and is speculative. Lacking a systematic testing, it cannot be stated that these patients are different, that they would not have had the same benefit from aspirin, or that they did not enjoy a spontaneous improvement in their arthritis.

Ankylosing Spondylitis

In patients with ankylosing spondylitis indomethacin in a dairly dose of 50 to 100 mgm has proven an effective measure for relief of pain. Although there are no controlled studies, the common experience of rheumatologists is in agreement that it is as effective as phenylbutazone in the treatment of spondylitis. In efficacy, equivalent dosage (i.e., the number of capsules required for relief of symptoms) and the tendency for gastro-intestinal irritation, the two medicines seem to be equal. Thus the choice of one or the other for the management of a spondylitic would depend upon the individual patient's preference or response.

Gout

Indomethacin is very effective in the treatment of acute gouty arthritis. Smyth *et al*[5] treated seven patients with large doses (600 to 800 mgm the first day) and demonstrated objective evidence of improvement in all within 24 hours. Boardman and Hart[6] obtained an excellent response with a lesser dose of 75 to 100 mgm a day. Although they felt that indomethacin was preferable to phenylbutazone or colchicine in their patients, most observers regard the drugs as equally effective in gout. Either indomethacin or phenylbutazone is preferable to colchicine for acute attacks of known or proven gout, since the distressing nausea and diarrhea that accompany the traditional hourly colchicine tablets can be avoided.[6a] The possible value of daily indomethacin in preventing recurrent attacks of gouty arthritis has not been assessed.

Osteoarthritis of the Hip

It has been reported that indomethacin often relieves the pain of degenerative hip disease in patients who have not been helped by aspirin. This is a puzzling effect since the drug is not nearly so beneficial in degenerative disease of other joints, such as the knee. When compared with the placebo in a crossover study, indomethacin (75 to 150 mgm a day) was preferred by 14 of the 18 patients taking part.[7] The evidence that it is more effective than phenylbutazone is less convincing. In one study, 11 patients preferred indomethacin, 7 phenylbutazone.[8] Further comparisons of these two drugs are needed.

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[5] Smyth, C. J., Velaynos E. E. and Amoroso, C.: Act. rheum. scandinav, *9*: 306, 1963.

[6] Boardman, P. L. and Hart, F. D.: Practitioner *194*: 560, 1965.

[6a] It should be mentioned, however, that the early *intravenous* administration of colchicine (2 mgm) produces little if any nausea and diarrhea and is often highly effective in the relief of acute gouty arthritis.—Ed.

TOXICITY

Indomethacin is a relatively safe drug. There are two main areas of potential toxicity: gastrointestinal distress and peptic ulcer, headache and other cerebral disturbances. The reports of hepatitis, uremia, pancreatitis and leukopenia are so infrequent that these perhaps represent coincidence. Rash and urticaria are infrequent.

It has become apparent that gastriontestinal ulceration and salt retention are invariably observed to some degree with all anti-inflammatory agents currently known. The gastrointestinal disturbances range from dyspepsia through nausea, pain and occult bleeding to peptic ulceration. Reliable comparisons of relative ulcerogenicity pose a tedious task and none have been made. Indomethacin appears to be no better and no worse than salicylate, phenylbutazone or corticosteroid when used in equipotent therapeutic doses. The gastrointestinal ulcerations have been demonstrated in animals given indomethacin orally, intravenously and rectally. Therefore the use of rectal suppositories, in itself a dubious routine for ambulatory patients, offers no advantage. Edema due to salt and water retention has been observed with indomethacin but rarely.

Headache and other central nervous system symptoms represent the most common side effects peculiar to indomethacin. The headache is of variable nature; usually it is described as frontal, throbbing, most severe in the morning on awakening. Its frequency varies in different studies, probably depending on dose. An indication of the problem involved in the evaluation of this complaint can be gathered from the controlled studies wherein about 50% of the drug-treated patients, versus 25% of the placebo groups, admitted to headache. In most patients taking indomethacin, the headache was severe enough for them to stop the drug or decrease the dose.

The other cerebral symptoms reported are dizziness, giddiness (light-headedness), muzziness (mental confusion). Depression, drowsiness, hallucinations, seizures and syncope are reported rarely, and it is not possible to determine if they are truly related to the drug.

Boardman and Hart[9] found headache was the main complaint at high dosage (2.9 mgm/kg—about 200 mgm) and muzziness the most common at low dosage (1.1 mgm/kg—about 75 mgm). They suggest that both may be the result of a common effect of the drug in the central nervous system. The pathogenesis of the headache and other symptoms is unknown. Indomethacin may alter the reactivity of the cerebral arterioles causing vasoconstriction and reflx vasodilation, but the experimental evidence for this is unconvincing. Both the headache and other symptoms improve rapidly when indomethacin is discontinued.

There have been a few reports suggesting that indomethacin may interfere with the normal resistance to infection. Jacobs reported two children withs juvenile rheumatoid arthritis who were receiving indomethacin and other medications and who died suddenly of overwhelming infection.[10] Although such instances are few, it may be significant that in testing in animals an increased incidence of spontaneous infections was noted in rabbits, dogs and guinea pigs. For the present it is recommended that indomethacin not be administered to children.

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[7] Wanka, J. and Dixon, A.: Ann. Rheum. Dis. 23 : 288, 1964.
[8] Zachariae, E.: Nord. med. 75 : 384, 1966.
[9] Boardman, P. L. and Hart, F. D. : Ann. Rheum. Dis. 26 : 127, 1967.
[10] Jacobs, J. C.: J.A.M.A. 199 : 932–934, 1967.

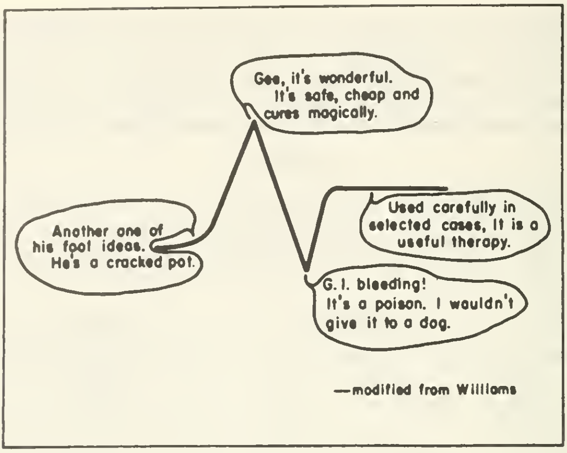
Gee, it's wonderful. It's safe, cheap and cures magically.
Another one of his fool ideas. He's a cracked pot.
Used carefully in selected cases, it is a useful therapy.
G. I. bleeding! It's a poison. I wouldn't give it to a dog.
—modified from Williams

FIG. 2.—COURSE OF THE PHYSICIAN'S RESPONSE TO INTRODUCTION OF NEW DRUGS.

SUMMARY

Indomethacin represents an entirely new class of compounds, indole-acetic acid derivatives, which has demonstrated anti-inflammatory activity. Although it is not related chemically to salicylate, steroid or the pyrazoles, it possesses the same propensity to gastrointestinal ulceration and salt retention shown by those compounds.

Its therapeutic profile is remarkably similar to phenylbutazone; it provides excellent relief in ankylosing spondylitis and acute gouty arthritis. In rheumatoid arthritis, the potency of indomethacin is comparable to that of aspirin. It also seems to relieve the pain of degenerative arthritis of the hip. For the most part a safe drug, its main side effects are gastrointestinal irritation and reversible central nervous system effects, headache, dizziness and muzziness.

It seems that the oscillations in enthusiasm for any new drug charted by Williams[11] in 1954 are equally true of indomethacin today (see Fig. 2).

L. A. HEALEY, M.D., *Seattle, Wash.*

(Whereupon, at 1:10 p.m., the hearing was recessed, to reconvene at 10 a.m., Wednesday, April 24, 1968.)

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[11] Williams, R. H.: J.A.M.A. 156: 127–136, 1954.

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, APRIL 24, 1968

U.S. Senate,
Monopoly Subcommittee of the
Select Committee on Small Business,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:05 a.m., in room 2221, New Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Our first witness is Dr. Robert Pinals. Dr. Rodnan is unable to be here today, so Dr. Pinals will be our only witness this morning.

STATEMENT OF DR. ROBERT S. PINALS, DIRECTOR, ARTHRITIS UNIT, LEMUEL SHATTUCK HOSPITAL, BOSTON, MASS.

Senator Nelson. Doctor, did you submit a biographical background for the committee record?

Dr. Pinals. No. I do not believe I did, sir.

Senator Nelson. If you wish to, you may give your medical credentials, background, for the record. The committee is very pleased that you took the time to come here this morning. We appreciate your making a contribution to these hearings.

Dr. Pinals. I am at present director of the arthritis unit at Lemuel Shattuck Hospital in Boston, and Assistant Professor of Medicine at Tufts University.

Senator Nelson. You may put whatever you would like in the record as to your background.

Dr. Pinals. I think that is it.

Senator Nelson. Fine. You may go ahead and present your statement. I assume you have no objection to interruptions for questions.

Dr. Pinals. Not at all, sir.

Senator Nelson. Fine.

Dr. Pinals. Indomethacin has been shown to be effective in the treatment of several rheumatic diseases including gout, ankylosing spondylitis (which is a form of spinal arthritis usually affecting young men), and degenerative arthritis of the hips. Having some significant advantages over other drugs used to treat these conditions, indomethacin has proved to be a useful addition in their management.

Senator Nelson. May I interrupt a moment, Doctor? Have there been double-blind trials with this drug on gout?

Dr. Pinals. There have not, as far as I am aware, been double-blind trials on gout. I might add parenthetically, though, that to my knowledge, there have never been any double-blind trials on gout with any drug.

Senator Nelson. There have not?

Dr. Pinals. No.

Senator Nelson. How does one measure the effectiveness, then, of a drug without this kind of a trial? To put it another way, what evidences did the company submit at the time of their New Drug Application to indicate efficacy respecting gout?

Dr. Pinals. You mean with respect to indomethacin?

Senator Nelson. Yes.

Dr. Pinals. I think it was just a series of cases treated by recognized specialists in gout, these cases having responded to the medicine, just on simple observation.

I do not think studies have extended any further than that.

Senator Nelson. I see. Have there been any on spondylitis?

Dr. Pinals. I think there have been two controlled studies on spondylitis.

Senator Nelson. Are you familiar with those studies?

Dr. Pinals. I do not have them right here at the moment, but they have been just recently published. One study compared indomethacin with another drug in common use in spondylitis and showed it to be about the same in efficacy as this other drug which is named phenylbutazone. In another study indomethacin was found to be superior to placebo.

Mr. Gordon. In an article that was submitted for the record by Senator Scott yesterday from the Bulletin on Rheumatic Diseases, it was stated that—

> The possible value of daily indomethacin in preventing recurrent attacks of gouty arthritis has not been assessed.

And it also says here—

> Although they felt that indomethacin was preferable to phenylbutazone or colchicine in their patients, most observers regard the drugs as equally effective in gout.

Does that sound reasonable to you?

Senator Nelson. It is an article by L. A. Healy, in Seattle, Wash.

Dr. Pinals. Yes. In the treatment of gout drugs are given for two different purposes. One, to prevent attacks, and another to treat attacks once they have started.

In the first regard, the standard drug has always been colchicine and this is taken in a certain dose every day, the aim being to prevent attacks from occurring. Indomethacin has been recommended for use in a similar way but it has not been, I do not think, studied in a controlled fashion or compared to colchicine. There are those who think it works in this manner. One might also add that colchicine which is a very old drug, having been used since the 6th century, has never been subjected to a double-blind trial.

Mr. Gordon. Also, I notice with regard to osteoarthritis of the hip it is stated in the same article that Senator Scott submitted:

"The evidence that it is more effective than phenylbutazone is less convincing."

Dr. PINALS. I am not aware of any comparative studies in osteoarthritis of the hip between those two drugs. I may have forgotten. My own impression is that the two drugs are probably about equally effective in osteoarthritis of the hip.

Mr. GORDON. Thank you.

Dr. PINALS. Although indomethacin is fairly effective as a drug to give pain relief in a variety of minor illnesses and to lower temperature in various conditions which result in a fever, it should probably not be used in such a manner because other drugs which work just as well and give few side effects are available. In fact, Merck Sharp & Dohme recommends in their promotional literature that indomethacin not be used for this purpose. It is mainly in the treatment of rheumatoid arthritis that its effectiveness has been questioned.

Rheumatoid arthritis is a crippling and disabling inflammatory disease of the joints. Its cause is unknown and its treatment has always been unsatisfactory. Over the years many new medications and treatments have been introduced with claims of striking benefit, only to be dropped later. The reason for this initial enthusiasm and later disappointment are in part psychological.

The hope and optimism which accompany a new medicine may allow patients to deceive themselves and their physicians into believing that they are really being helped. Many arthritics, perhaps as many as 50 percent, feel that they get some relief even when the new medication given is a placebo. However, another factor which makes evaluation of new treatments difficult is that the disease itself often waxes and wanes. Even without treatment there may be periods of remission. If a new medicine had been given at these times, great benefits might have been ascribed to it. For these reasons it is important that trials of new drugs in rheumatoid arthritis be carefully controlled, usually using the so-called double-blind technique. With this type of testing neither the patient nor the physician knows whether the new drug or a placebo or older drug is being given until the trial is over, thus eliminating most sources of bias. The standard drug which almost all rheumatoid arthritis patients take is aspirin. It is relatively safe and inexpensive. Therefore, if any new medication is to be introduced as a treatment it would be reasonable to find out whether it works as well as or better than aspirin. Cortisone is more potent than aspirin but its use is limited by dangerous side effects. During the last 15 years pharmacologists have been searching unsuccessfully for a drug which would duplicate the benefits possible with cortisone without the undesirable side effects.

Senator NELSON. Despite the side effects, what kind of beneficial results does one get from the administration of cortisone?

Dr. PINALS. Cortisone gives very dramatic and usually rapid decrease in the swelling of the joints in rheumatoid arthritis and it relieves the pain and stiffness. It is possible if enough cortisone is used in an early case of rheumatoid arthritis, to remove all signs of the disease. Not in all cases but in many cases.

Senator NELSON. Permanently?

Dr. PINALS. Not permanently. When the drug is stopped, usually very quickly, within a matter of a few days, the disease returns, often in a worse form than previously. It does not cure the disease at all. In fact, there is no evidence that even prolonged use of this drug makes any difference in the long-term end result. In other words, the patient may have just as much destruction of the joints, just as much crippling and deformity having taken cortisone for many years as he might have otherwise.

Senator Nelson. Is there any evidence that any drug arrests the progress of the disease in any permanent way?

Dr. PINALS. I would say not. There have been a number of drugs studied in rheumatoid arthritis using good double-blind techniques. The improvement noted in these studies, though, has been temporary. The fact is, though, that no really long-term controlled studies have ever been done. I think 3 years is the longest that a proper study has been carried out.

Senator NELSON. So, there is no way to determine whether or not the use of a particular drug makes any difference in the progress of the disease over a 10- or 15-year period, is that correct?

Dr. PINALS. That is correct. There are those who feel that certain drugs do, but there is no evidence to support it.

Mr. GORDON. Doctor, is rheumatoid arthritis more common than the other diseases in which indomethacin is useful?

Dr. PINALS. Yes. I would say that it is about three or four times more common than gout and about 10 times more common than ankylosing spondylitis.

Mr. GORDON. You also state here:

> The hope and optimism which accompany a new medicine may allow patients to deceive themselves and their physicians into believing that they are really being helped. Many arthritics, perhaps as many as 50 percent, feel that they get some relief even when the new medication given is a placebo.

Now, does that mean the cards are stacked in favor of any drug by at least 50 percent to start with because of this placebo effect?

Dr. PINALS. Yes, indeed. If the drug is not studied in a controlled or double-blind manner, some of the apparent effect of the drug may be really a so-called placebo effect.

Mr. GORDON. In addition, since the disease waxes and wanes, as you state, since it is psychological in nature, the patient is going to get better anyhow and we start off with another bias in favor of the drug. Is that correct?

Dr. PINALS. I think that is true. In general doctors tend to use new drugs more often when the disease is at its worst. They do not start a new drug when the patient has temporarily improved. Therefore, in the case of those patients who will subsequently improve on their own, a new drug started at the time when they are bad might lead to the impression that the drug itself was helping rather than that improvement was related to just the natural course of the illness.

Mr. GORDON. Would it be fair to say, then, Doctor, that outside of the double-blind, carefully controlled test, a statistical compilation of the effectiveness of a drug for this disease is really not too meaningful? Would that be a fair statement?

Dr. PINALS. I think within limits that would be a very fair statement. Unless a drug seems to be almost totally successful in a disease like rheumatoid arthritis, double-blind studies are probably needed. Cortisone was never studied in a double-blind manner. One of the reasons is that it was introduced during an era when such studies were not being done. However, it probably would not have been necessary to study cortisone in that way because it almost, at least as far as its short-term effect is concerned, it almost always works in a very effective manner if enough is given. The long-term effects are another matter.

The development of indomethacin in the research laboratories of Merck Sharp & Dohme was a part of this effort. When tested in animals it appeared to suppress inflammation as well as or better than cortisone. It was used for over 5 years in preliminary studies in human volunteers and later in over 5,000 patients with arthritis and other conditions before its approval by the FDA, in June 1965. This approval was, of course, based on the accumulation of evidence establishing the safety and efficacy of the drug. Even now, with a retrospective view of 3 years, I believe the FDA decision was justified. Indomethacin produces side effects quite frequently, perhaps in about a quarter to a half of patients who take it, depending upon the dose and duration of treatment. These side effects were well known when the drug was introduced in 1965 and no important new ones have been added during the last 3 years. Although frequent, the reactions are not dangerous and disappear when the drug is withdrawn or the dose reduced. They can be divided into two general categories: (1) Central nervous system effects—headache, dizziness, drowsiness; (2) gastrointestinal symptoms—nausea, vomiting, diarrhea, and abdominal pains. It is suspected that indomethacin may occasionally contribute to the formation of stomach ulcers but this has not been proven. Most other drugs used in the treatment of arthritis also have or are suspected of having this undesirable capability.

The evidence for efficacy of indomethacin when it was introduced for general use in 1965 included many studies by competent physicians, but very few which were strictly controlled utilizing the double-blind technique which I mentioned previously. Several of these studies were in progress at the time but the results were not available until about a year later. This was not an unusual situation in the early 1960's. Double-blind studies were the exception rather than the rule. They were usually not done early in the investigational process and often only if some doubt arose as to the efficacy of the drug. At the present time there is a growing tendency to do these studies earlier and more frequently. One must keep in mind that such studies are not performed by the pharmaceutical house but by physicians who are interested in using the drug and learning more about its effects. Our own study compared indomethacin and aspirin in a group of patients who took each drug for 1 month in a double-blind fashion. We found no significant difference between their effects on the signs and symptoms of arthritis. Several other studies have now been done in this country and in England. Some of these have failed to show any benefit from indomethacin as compared to a placebo in rheumatoid arthritis. Others have shown indomethacin superior to placebo but the differences have not been large.

I would like to point out that our techniques for measuring improvement or worsening in arthritis are not very precise as compared to experiments done on animals in the laboratory. A drug would have to be quite a bit better than a placebo before the difference would be appreciated using these techniques. One might draw an analogy to measuring the difference in weight between a lemon and a grapefruit. Using a sensitive balance this would be easy, but using a bathroom scale it would be difficult or impossible. Therefore, one should not properly conclude from these studies that indomethacin is no better than a placebo but that if it is effective the benefit is too small to be appreciated with existing techniques.

Senator NELSON. May I ask a question at this stage? Were all of these double-blind trials done with aspirin being used in both the test group and the control group?

Dr. PINALS. No. I believe that my trial and two others were done with aspirin. The others were done with placebo, comparing Indocin and placebo.

Senator NELSON. I do not have the testimony here, but the trials that Dr. O'Brien referred to in his testimony yesterday all involved a placebo and aspirin and indomethacin and aspirin.

Dr. PINALS. I think all of the studies used either placebo or aspirin as a comparison with indomethacin. I do not think any of the studies have used all three together.

Senator NELSON. No. What I meant to say, as I recall Dr. O'Brien's testimony, is that all of the double-blind trials that he referred to and discussed yesterday, involved about half the patients on a placebo and aspirin and the other half on indomethacin and aspirin.

Dr. PINALS. Oh, yes. That was the trial done by Dr. Mainland's group. All of the patients in the study were taking aspirin but half were taking indomethacin and half were taking placebo in addition to the aspirin. Yes.

In the case of our study, the patients took indomethacin 1 month without aspirin and for the second month took only aspirin without indomethacin. There was no placebo involved.

Senator NELSON. And, what differences did you find during the month in which the patients had only aspirin compared with the month in which they had only indomethacin?

Dr. PINALS. We found they were about the same.

Senator NELSON. Then, would it not be correct according to the last sentence you read saying that a drug would have to be quite a bit better than a placebo before the difference would be appreciated using these techniques, it may very well be, might it not, that aspirin is better than indomethacin, but you cannot measure that, either?

Dr. PINALS. Yes. In fact, I believe that to be true. In our study the aspirin did appear to be a little better than indomethacin but the differences were not significant statistically. Perhaps if we had used more patients, the differences might have been more appreciable. For the most part all of these studies have been done using similar techniques of measurement.

Dr. Mainland's group in the past has done a study comparing placebo to aspirin and found that the aspirin was better than placebo, although not by a great deal. His group also compared Indocin to placebo and found them not to be different. Our study found aspirin and Indocin to be about the same. Putting all these three together, I would probably rate these three drugs in the order of effectiveness as aspirin first, indomethacin second, and placebo third. I would rate indomethacin somewhere between aspirin and placebo in its effectiveness in rheumatoid arthritis.

Senator NELSON. Please go ahead.

Dr. PINALS. Such studies also draw conclusions which would relate to the majority of cases or to the average case since all of the results are pooled for statistical analysis. If only a few cases out of the total group of arthritics are capable of a good response to indomethacin, the studies would not reveal this.

In reviewing all of the studies in the light of my experience I would conclude that indomethacin is a valuable agent for several rheumatic disorders but not for most patients with rheumatoid arthritis, who would do just well or better taking aspirin. I believe that even in rheumatoid arthritis, indomethacin is better than a placebo but that the differences may be too small to measure with existing techniques. In a few cases indomethacin seems to have a very dramatic beneficial effect. Since this can only be determined by a short trial on the drug I see no objection to its use in occasional difficult cases but such trials will usually be unsuccessful.

Although I know very little about drug advertising or its impact, I would guess that the size of the campaign promoting a particular product would be related to the cost of research and development and to the magnitude of the potential market. In the case of indomethacin the basic research effort was large and also, I might add, very well done. The market, or the number of patients who might use a potent and safe anti-inflammatory drug, is huge. On this basis one would expect a fairly large promotional campaign. I do not believe the advertising has been deliberately misleading and see no reason to doubt that the company acted in good faith. In 1965 almost everyone believed, on the basis of the information available at that time, that indomethacin might prove to be a very important therapeutic agent in rheumatoid arthritis. The advertising reflected this impression. Recent advertising has been more restrained, also reflecting the current state of our knowledge.

Indomethacin is not the first drug which has not entirely fulfilled its early promise, nor will it be the last. One way to prevent future disappointments of this sort would be to perform well-controlled clinical trials early during the period of investigation rather than later. Again, I would point out that the value of this approach has only recently been recognized by the medical profession which must bear the ultimate responsibility for putting it into practice.

Senator NELSON. Thank you, Doctor. For the record, we will include at the conclusion of Dr. Pinals' testimony an article by him on this subject which appeared in the New England Journal of Medicine and an article from the British Medical Journal on this subject.

Mr. GORDON. Dr. Pinals, in the 1966 edition of New Drugs, AMA's publication, there is the following statement on page 532: "Indomethacin should be regarded as potentially ulcerogenic, although the available evidence on this point is contradictory." That is in 1966.

In 1967, however, on page 540, we find the following statement: "Indomethacin should be regarded as being potentially ulcerogenic." It leaves out the phrase, "although the available evidence on this point is contradictory." That provision is no longer included.

Then, in asterisks it makes the following statement: "It may produce single or multiple ulcerations of the esophagus, stomach, duodenum or small intestine. Cases of perforation and hemorrhage, a few of them fatal, have been reported."

Now, there is quite a difference between the 1966 statement and the 1967 statement. Can you tell us what happened in that period to cause the addition of this rather vigorous warning?

Dr. PINALS. Yes. I do not know the basis for the change in opinion in that particular book. However, I might say that a number of studies with indomethacin have shown a fairly high incidence of ulcers in the stomach. Other studies have shown a fairly low incidence.

To my knowledge, there has been no study in which ulcers were looked for before the drug was given and then looked for again after the drug was given. We are dealing here with a group of patients who are very prone to get ulcers anyway and many of the other drugs that are given for rheumatoid arthritis can also cause or have been accused of causing ulcers. That includes cortisone and its derivatives, aspirin, phenylbutazone. Many of the patients have been taking these other drugs at the same time that they have been taking the indomethacin. So, I would submit that although I think my impression would be that indomethacin may cause ulcers, I do not think the point has been proven at all.

I think this sort of side effect should be approached in a controlled way, in the same way that one looks for evidence of efficacy of the drug. And to my knowledge, it has not been done yet.

Mr. GORDON. Well, the law states that before a drug is put on the market, substantial evidence of safety and efficacy must be supplied. Now, if there is no evidence of safety based on controlled studies, would you say there is substantial evidence that this provision of the law has been met with respect to this particular drug?

Dr. PINALS. I think that the evidence that was available in 1965, both for the efficacy and for the safety, was, as far as quality was concerned, as good as or better than other drugs that were introduced at about that time or previously. I think that in the light of what we know now and in regard to our present attitudes toward investigation of drugs, we would not hold that same opinion. We would insist that drugs be introduced now or in the future on better evidence, both for efficacy and for safety. But, I would say that indomethacin, when looked at in a comparative way, stacks up pretty well compared to other drugs used for arthritis and drugs used to treat other conditions insofar as the type of studies that were done and the evidence for safety.

Senator NELSON. Do I understand you correctly to be saying that so far as the evidence submitted with the New Drug Application for indomethacin was concerned, at the time it was filed, considering the standards required by the FDA, this one was as good a submission of evidence and perhaps better than many others that were being accepted at that time? Is that what you are saying?

Dr. PINALS. Yes, Senator. I believe that although I have never seen the FDA's requirements or standards written down, I know that drugs were introduced in the early sixties and previously without the benefit of controlled studies of the sort that we have been discussing. In fact, these types of studies were extremely rare.

Mr. GORDON. As I understand it, Doctor, you would insist now that double-blind studies be performed with respect to safety and efficacy?

Dr. PINALS. I think if indomethacin were introduced today, not only would I like to see such studies but I have a feeling that the pharmaceutical houses would as well and are making presently greater efforts to see that such studies are done.

Senator NELSON. Thank you very much, Doctor. We appreciate your taking the time from your busy schedule to come here from Boston and testify. You have made a very valuable contribution to our hearing record.

Dr. PINALS. Thank you.

Senator NELSON. The next hearing will resume on May 1 in room G308 of the New Senate Office Building.

(The articles previously referred to follow:)

[From the New England Journal of Medicine, Mar. 2, 1967, pp. 512–514]

MEDICAL INTELLIGENCE—RELATIVE EFFICACY OF INDOMETHACIN AND ACETYLSALICYLIC ACID IN RHEUMATOID ARTHRITIS*

(By Robert S. Pinals, M.D.,† and Sumner Frank, M.D.‡)

BOSTON.—Indomethacin, a new anti-inflammatory and analgesic drug, has been used in the treatment of a great variety of rheumatic disorders. To place a new agent in proper therapeutic perspective, controlled studies must be done to compare it with medications already in use for each disease. To investigate the relative effectiveness of indomethacin and acetlysalicylic acid in patient with rheumatoid arthritis we have performed a double-blind, crossover trial in which both drugs were given for one month in random order, to each patient. Since it has been suggested that indomethacin be administered initially in small doses to minimize side effects, a schedule of gradually increasing dosage was used during both months. Determinations of subjective and objective response were made at the middle and end of each month.

MATERIAL AND METHODS

Twenty-four out-patients with definite or classic rheumatoid arthritis entered the study; 13 were female. The mean age was fifty-three years (range, twenty-three to sixty-nine years). All had been receiving salicylates. In addition, 5 patients had been taking small doses of corticosteroids (less than 10 mg. of prednisone or its equivalent); no change was made in this dose during the study. Identical capsules containing indomethacin, 12.5 mg., or acetylsalicylic acid, 400 mg., were taken four time a day. The daily dosage schedule during each month was as follows: in the first week, indomethacin, 50 mg. or acetylsalicylic acid, 1.6 mg.; second week, indomethacin, 100 mg., or acetylsalicylic acid, 3.2 mg.; third week, indomethacin, 150 mg., or acetylsalicylic acid, 4.8 mg.; and fourth week, indomethacin, 200 mg., or acetylsalicylic acid, 6.4 mg. The order of drug administration was determined from a table of random numbers and was unknown to the examiners. Of the 21 patients who completed both months of the trial 10 received indomethacin during the first month. To prevent the acute exacerbations of arthritis that may follow sudden withdrawal of salicylates,[1] all patients took acetylsalicylic acid, 1.8 mg. daily (or the equivalent amount of the salicylate preparation used prior to the study), during the first week of each month, in addition to the trial medication. After the first week no additional salicylates were allowed. In a few cases the dosage was reduced during the final week of the month because side effects. Instead of the scheduled dose of 16 capsules daily, the actual dose of acetylsalicylic acid was 12 to 13 capsules in 4 and 14 to 15 capsules in 3 patients. With indomethacin the dose was 12 to 13 capsules daily in 2 and 14 to 15 capsules in 1.

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[1] Fremont-Smith, K., and Bayles, T. B. Salicylate therapy in rheumatoid arthritis. *J.A.M.A.* 192: 1133–1136, 1965.

Evaluations were made at intervals of two weeks and included the sedimentation rate (Westergren method), grip strength, determined in the standard manner[2] by the same person (a research nurse), the average of 3 squeezes with each hand on a sphygmomanometer cuff being taken as the final figure, and articular score. Joints were examined on each evaluation visit by the same physician. One point was given for tenderness or pain on motion and additional points for soft-tissue swelling and heat in each joint. Thus a single joint might contribute 3 points to the total score. The spine, hips and interphalangeal joints of the toes were not included because precise examination is difficult. Another criterion was patient preference. Patients were told before the trial that the capsules would contain a different medication during the first and second months of study. At the conclusion each patient was asked whether symptoms of arthritis were the same during both months or better during one or the other. Finally, the physician's evaluation was included. Before the code was broken, the physician expressed his opinion of which medication was superior, and attempted to guess, on the basis of side effects, the order of drug administration.

For statistical analysis the differences in various parameters at the evaluations at two and four weeks for each monthly trial period were subjected to a "t"-test.

RESULTS

Three patients, all female, did not complete the trial. One was eliminated during the first week when intestinal obstruction, later found to be due to cancer, developed. Two patients dropped out because of intolerable side effects, even at reduced doses of the trial medication. One was taking indomethacin at the time, and 1 acetylsalicylic acid. Data from these 2 cases are not included in the evaluation results, but are included in the summary of side effects.

There was no significant difference between the 2 medications in their effect upon grip strength, articular score and sedimentation rate (Table 1). In subjective terms neither drug had the advantage. Seven patients preferred indomethacin, and 7 acetylsalicylic acid, and the remaining 7 could detect no difference. The physician's evaluation showed indomethacin superior in 5 patients, acetylsalicylic acid in 6 and no difference in 10. There were no obvious clinical characteristics by which the patients responding better to either drug could be identified.

TABLE 1.—MEAN VALUES IN 21 PATIENTS WHO COMPLETED THE TRIAL

Drug	Sedimentation rate [1]	Grip strength [1]	Articular score [1]
Indomethacin:			
At 2 weeks	54.6±6.91	135.1±13.50	26.9±3.24
At 4 weeks	58.0±6.60	139.5±13.52	25.7±2.38
Acetylsalicylic acid:			
At 2 weeks	54.4±5.94	134.3±13.12	25.9±2.45
At 4 weeks	50.9±6.46	137.1±13.19	23.6±2.39

[1] Mean±standard error of mean.

TABLE 2.—SEVERITY OF SIDE EFFECTS IN 23 PATIENTS[1]

[Number of patients]

Degree of side effects	Indomethacin		Acetylsalicylic acid	
	At 2 weeks	At 4 weeks	At 2 weeks	At 4 weeks
None	14	6	15	3
Mild or moderate	8	13	6	13
Severe	1	3	1	5

[1] 2 patients who withdrew from trial because of side effects included in this tabulation.

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[2] Cooperating Clinics Committee of American Rheumatism Association. Seven-day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis & Rheumatism* 8: 302–335, 1965.

The frequency and severity of side effects (Table 2), was virtually the same at the dosage levels employed in this study. There was a qualitative difference, acetylsalicylic acid caused more tinnitus and deafness and indomethacin more headaches (Table 3). Since the frequent occurrence of side effects typical of one or the other drug might compromise the double-blind character of the study an attempt was made to determine the magnitude of this possible source of bias. The observers tried to predict the order of drug administration on the basis of side effects. This prediction was correct in the 2 patients who dropped out of the study. Among the 21 who completed the trial, no prediction could be made in 11. Of the remaining 10 the guess was correct in only 6. Although headache and tinnitus, symptoms typically associated with indomethacin and acetylsalicylic acid, respectively, were noted frequently, the mildness and inconstant nature of these side effects in most cases did not allow correct identification of the trial drug. Several patients had headache and tinnitus during the same month. The nurse and technician who measured grip strength and sedimentation rate were uninformed about the side effects, thus limiting the possibility of bias to the articular score and subjective evaluations was limited.

DISCUSSION

Before its introduction into clinical use, indomethacin was shown to be an excellent suppressor of granulomatous inflammation in laboratory animals, exceeding even hydrocortisone in potency.[3] Expectations of an effect of this order on a similar type of inflammatory process in a human pathologic state, such as rheumatoid arthritis, have not been fulfilled. Most of the early, uncontrolled experience with this new agent suggested a beneficial effect in rheumatoid arthritis,[4 5 6] but the dramatic changes that often follow administration of large doses of corticosteroids were seldom observed. In controlled studies indomethacin was shown to be superior to a placebo[7] and not significantly different from phenylbutazone[8] in the treatment of rheumatoid arthritis.

TABLE 3.—TYPES OF SIDE EFFECTS

Side effect	Patients receiving indomethacin			Patients receiving acetylsalicylic acid		
	Mild or moderate	Severe	Total	Mild or moderate	Severe	Total
Epigastric distress, heartburn, and abdominal pain	6	1	7	7	1	8
Headache	8	1	9	1	1	2
Dizziness and vertigo	1	1	2	2	2	4
Tinnitus and deafness	4	1	5	13	1	14
Nausea and vomiting	2	0	2	1	1	2
Rash and pruritus	2	0	2	0	0	0
Restlessness, agitation and anxiety	0	1	1	0	1	1
Somnolence and confusion	0	0	0	0	1	1
Dry mucous membranes	0	0	0	3	0	3
Diarrhea	3	0	3	0	0	0

It then became necessary to compare indomethacin with acetylsalicyclic acid, the drug most widely used in the management of this disease. Our results indicate that indomethacin has no advantage over acetylsalicylic acid. In a single-blind, crossover study with administration of each drug for 2 weeks in doses smaller than those that we have used, Pitkeathly et al.[9] found no large differences in effectiveness between the 2 medications. Although grip strength improved to a greater extent on indomethacin patient preference was greater for acetylsalicylic acid.

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[3] Winter, C. A., Risley, E. A., and Nuss, G. W. Anti-inflammatory and antipyretic activities of indomethacin, 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. *J. Pharmacol. & Exper. Therap.* 141 : 369–376, 1963.

[4] Norcross, B. M. Treatment of connective tissue disease with new non-steroidal compound (indomethacin). *Arthritis & Rheumatism* 6 : 290, 1963.

[5] Catoggio, P. M., Centurion, A., Alberti, H., Roldan, H., and Canepa, L. Indomethacin in rheumatoid arthritis : properties, side-effects. *Arthritis & Rheumatism* 7 : 300, 1964.

[6] Rothermich, N. O. Indomethacin : new pharmacologic approach to management of rheumatoid disease. *Arthritis & Rheumatism* 6 : 295, 1963.

[7] Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St. J. Indomethacin in rheumatic diseases : controlled clinical trial. *Ann. Rheumat. Dis.* 23 : 218–225, 1964.

[8] Hart, F. D., and Boardman, P. L. Indomethacin and phenylbutazone : comparison. *Brit. M. J.* 2 : 1281–1284, 1965.

[9] Pitkeathly, D. A., Banerjee, N. R., Harris, R., and Sharp, J. Indomethacin in in-patient treatment of rheumatoid arthritis. *Ann. Rheumat. Dis.* 25 : 334, 1966.

The possibility that more prolonged administration of indomethacin is necessary for better "anti-rheumatic" action cannot be excluded. However, in experimental-model inflammatory systems its effect has been rapid.[3] Likewise, in the treatment of other rheumatic conditions, such as gout and ankylosing spondylitis, its beneficial action is said to take place within hours or days. Although favorable reports of its efficacy in these 2 disorders have appeared[4 8 10] there have been no controlled studies. Investigators who have had considerable experience with the drug have found, as with phenylbutazone, a greater frequency of clinical improvement in ankylosing spondylitis and gout than in rheumatoid arthritis.[8, 10]

Ultimately, indomethacin may be found to be most valuable in the treatment of the part of the spectrum of rheumatic disease for which phenylbutazone is now used. Although some patients with rheumatoid arthritis may receive benefit from both indomethacin and phenylbutazone there seems to be no way to identify these patients *a priori* and, for the average case, no evidence that the effect will be superior to that obtained with a large dose of salicylates.

SUMMARY

In a double-blind study 24 patients with rheumatoid arthritis were treated with indomethacin and acetylsalicylic acid, each given for one month. Neither drug had a subjective advantage or superiority as determined by measurement of grip strength, sedimentation rate and number of tender and swollen joints. Side effects did not differ in frequency or severity, but headache was noted more commonly with indomethacin and auditory symptoms with acetylsalicylic acid.

(We are indebted to Dr. Hugo Muench, Rasma Klints, Carol Bellotti and Kenneth R. Haslam, M.D., of Merck Sharp and Dohme Research Laboratories, for assistance.)

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[10] Rothermich, N. O. Extended study of indomethacin. II. Clinical therapy. *J.A.M.A.* 195: 1102, 1966.

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Indomethacin in Rheumatoid Arthritis: An Evaluation of Its Anti-Inflammatory and Side Effects

(By Phelim Donnelly,[1] M.D., M.R.C.P.I., D. Phys. Med.; Kenneth Lloyd,[1] M.R.C.P.; Hubert Campbell,[2] M.A., M.B., B.S.)

Since its introduction in 1963 indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid) has been reported as an analgesic of value in the treatment of osteoarthritis (Hart and Boardman, 1963; Wanka *et al.*, 1964; Percy *et al.*, 1964) and ankylosing spondylitis (Katz *et al.*, 1963; Hart and Boardman, 1963; Smyth and Godfrey, 1964; Percy *et al.*, 1964; Rothermich, 1964; Michotte and Wauters, 1964; Boland, 1964), and as an agent that effectively reduces joint swelling and inflammation in acute gout (Hart and Boardman, 1963; Smyth *et al.*, 1963a, 1963b; Michotte and Wauters, 1964; Percy *et al.*, 1964; Norcross, 1963; Kåss, 1965). Similar though less striking results have been obtained with indomethacin in rheumatoid arthritis (Hart and Boardman, 1963; Norcross, 1963; Wanka *et al.*, 1964; Percy *et al.*, 1964; Catoggio *et al.*, 1964; Clark 1964; Rothermich, 1964; Datey, 1964; Smyth *et al.* 1964; Thompson, 1964; Smyth, 1965; Thompson and Percy, 1966). Kelly (1964a, 1964b) found the benefit "often astonishing," while boland (1964) was unable to demonstrate conclusively any effect of the drug on patients with rheumatoid arthritis. In the treatment of rheumatic fever Vignau *et al.* (1965) concluded that the advantages of indomethacin were outweighed by its side-effects.

A high incidence of side-effects in proportion to therapeutic effect with this drug in rheumatoid arthritis has been observed (Dixon *et al.*, 1963; Boland, 1964; Lövgren and Allander, 1964; Percy *et al.*, 1964; Boyle, 1965). Percy *et al.* (1964) had to withdraw 13 out of 21 patients taking 200 mg. each day, and

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Katz *et al.* (1965) withdrew 35 out of 97 patients on doses of 100 to 400 mg. a day, for this reason. Hart and Boardman (1963) reported side-effects in 31 out of 52 patients on a daily dose of 50 to 300 mg. Rubens-Duval and Villiaumey (1964) reported 72% side-effects in patients on a daily dose of over 200 mg., and Robinson (1965) could maintain therapy in less than 50% of patients receiving 125 to 150 mg. a day. On the other hand, Robecchi *et al.* (1964), using doses of 75 to 150 mg. each day, had only one withdrawal with 28 patients and found that though side-effects were frequent they were not unduly troublesome. These findings indicate that the therapeutic index of this drug is low.

Hart and Boardman (1963) demonstrated no greater efficiency with the higher range of dose and recommended 50–150 mg. as a satisfactory daily dose of indomethacin consistent with minimal side-effects.

PRESENT TRIAL

This trial was designed (1) to test the analgesic and anti-inflammatory effects of indomethacin in rheumatoid arthritis over a short term in a relatively low dose, and (2) to note the true incidence of side-effects.

Patients were accepted for the trial on the basis of active inflammation of six or more proximal interphalangeal joints of the fingers. This criterion was specified because of the ease of measurement of swelling and tenderness of these joints. Patients with flexion deformity of the fingers or firm non-tended thickening of the proximal interphalangeal joints resulting from long-standing joint changes were excluded.

Thirty patients with "classical" or "definite" rheumatoid arthritis were chosen (A.R.A. criteria, Ropes *et al.*, 1957). There were 18 women and 12 men aged 28 to 72, average 52.6 years, with disease of six weeks to 24 years' duration, averaging 8 years 2 months. The duration of disease in nine was from six weeks to four years, in 12 from five to nine years, and in nine for 10 years or more.

A number of patients were already receiving long-term drug therapy, and the dose of these drugs was unaltered during the period of the trial. Six were receiving hydroxychloroquine 600 mg./day, one was receiving oxyphenbutazone, and one Thylin (nifenazone). Adrenocorticosteroids had been given for the previous two years to two patients. One patient on weekly injections of 50 mg. of gold had received a total of 550 mg. of Aurothiomalate at the time of entry into the trial.

DESIGN

The trial lasted for ten weeks, including a "pre-trial" week at the beginning of which an assessment was carried out in order to accustom the patients to the trial procedure; these measurements were discarded. During this week two capsules of placebo were administered—a fact known to the examiner but not to the patient—with the intention of minimizing any placebo response by the time of entry into the trial proper at the end of this week when the first recorded assessment was carried out.

After this week the trial began, a double-blind crossover technique being used over two four-week periods, separated by a week during which all patients received two capsules a day of the placebo. This second placebo week was intended to minimize any possible "carry-over" effect of the drug into the placebo weeks in the group who received the active drug initially.

Indomethacin in standard commercial 25-mg. capsules was matched by a similarly coloured placebo powder (mainly lactose) in identical capsules sealed in similar containers. Two separate dose sequences were prepared. Patients in group 1 received indomethacin first for four week, followed by placebo for a further four weeks; those in group 2 received placebo followed by the drug. An incremental dosage scheme was adopted in order to reduce the incidence of side-effects (Hart and Boardman 1963, 1964; Suzman, 1964; Dilsen and Dilsen, 1964; Thompson, 1964). Each four-week period began with two capsules a day. The dose was then increased by one capsule a day at the beginning of each of the ensuing three weeks. Thus when indomethacin was administered the patients received a daily dose of 50 mg., 75 mg., 100 mg., and 125 mg. respectively during each of the four consecutive weeks (Fig. 1).

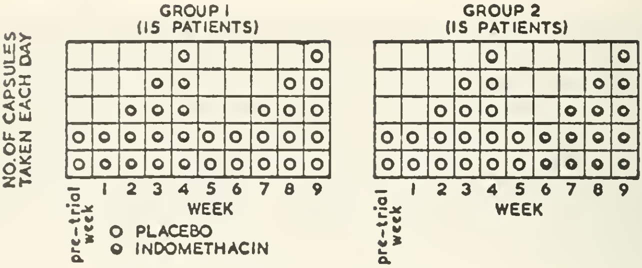

FIG. 1.—DOSAGE SCHEME OF TRIAL.

The patients were instructed to swallow the capsules with fluid, during or immediately after a meal, and were requested to return the container with any remaining capsules each week in order to receive their supply for the following week.

The first 30 patients examined in the outpatient clinic who fulfilled the criteria of the trial were accepted. They were numbered 1 to 30 consecutively as they entered the trial, each number having previously been allocated at random to either group 1 or 2.

ASSESSMENTS

Weekly assessments were carried out, the following criteria being used: (1) hand articular index, (2) pool of finger swelling, (3) systemic index (Lansbury, 1958), and (4) patient's opinion .

Hand articular index

The amount of small joint involvement of the hands was assessed by the presence of tenderness on firm palpation of the proximal interphalangeal and metacarpophalangeal joints, no attempt being made to grade the degree of tenderness present. The result was expressed as a sum of the number of joints so affected, the maximum possible being 20.

Pool of finger swelling

The degree of swelling of each proximal interphalangeal joint was recorded with jeweler's ring-gauges. These consist of a collection of 52 rings of graded sizes from the smallest labeled "A" through "A½" 'B" B½" to the largest "Z½." The circumference of all eight proximal interphalangeal joints and of the two thumb terminal joints, whether affected by arthritis or not, was determined by the smallest ring that could be passed over each joint. The letter size of the rings was equivalated numerically from 1 to 52; swelling too large to accommodate the largest ring was recorded as '53." Therefore the sum of the measurements of these 10 joints allowed a theoretical maximum score of 530.

Systemic index

This index was devised by Lansbury (1958) as a composite numerical expression of five characteristics of rheumatoid arthritis and is used as an indicator of activity of the disease. Its compilation utilizes five factors: (1) number of analgesic tablets taken each day, (2) duration of morning stiffness, (3) onset of fatigue, (4) strength of hand grip, and (5) E.S.R. (Westergren).

1. Patients were instructed to continue to take any analgesic tablets (usually aspirin) that they had already found effective and tolerable, but they were to regulate the dose and frequency of these tablets according to the demands of the pain. Put simply, "no pain, no tablets; much pain, many tablets; little pain, few tablets." This instruction was repeated each week and the patients were asked to record or remember the number of tablets taken daily, or the number per dose and the frequency of administration.

2 and 3. Patients were asked to note the duration of body stiffness after rising each morning and the length of time elapsing before the onset of fatigue every day.

4. Strength of grip was measured by using a folded rectangular rubber bag in a fabric cover measuring 12 by 6 cm. when deflated. This was connected to a spygmomanometer recording to 300 mm. Hg and inflated to a pressure of 20

mm. Hg with the valve closed. The height sustained by a single maximum-effort squeeze with each hand was recorded as the mean for both hands. Adequate rehearsal of the method was given at the pretrial examination.

Each of these estimations was accorded a number as indicated by reference to the standard table of Lansbury and the systematic index expressed as the sum of these numbers; the higher the number the more active is the arthritis.

Patients' opinion of the effectiveness of the capsule

This was judged by their general well-being and their feeling as regards their "rheumatic" symptoms over the week preceding. They were requested to express this as either "much better," "better," "no change," "worse," or "much worse." This was recorded each week as "+2," "+1," "—1," or "—2" respectively. In addition, at the end of the trial the patients were asked their opinion of the capsules and whether they wished to continue taking them.

In addition, on entering and leaving the trial two further assessments were carried out:

Functional grade.—Grades 1–5 were used as recommended by the Joint Committee of the M.R.C. (1954).

Articular Index.—This is a means devised by Lansbury to express numerically the total area of joint inflammation as indicated by tenderness or pain on passive movement. Joints are graded according to size and allocated appropriate numbers: the larger the point the higher the number; the higher the index the more extensive the arthritis. Thus comparison of total scores indicates expansion or contraction of the pool of joint inflammation.

These estimations entailed 2,740 separate observations which were made by one of us (P.D.) with the exception of 168 observations made over one two-week period.

SIDE-EFFECTS

The incidence and nature of side-effects were recorded weekly. Great care was taken not to inform the patients of any specific side-effect that might be expected, and they were not asked to report any untoward feelings or occurrences. No direct questions were put in this matter; the recorded side-effects were all elicited as a result of spontaneous remarks by the patients in the course of conversation about their general health and well-being.

Routine urine examination, haemoglobin estimation, and total white cell and differential counts were performed weekly. Serum albumin and globulin levels and electrophoretic differentiation, as well as thymol turbidity, flocculation, serum bilirubin, alkaline phosphatase, and glutamic and oxaloacetic transaminases, were performed at the conclusion on all patients completing the trial.

During the course of this trial Bruckner and Randle (1965) reported hepatotoxicity associated with the use of indomethacin. Because of this, further toxicity studies were extended beyond the trial period on those patients who continued taking indomethacin, and will be the subject of a separate communication.

RESULTS

Twenty-eight patients completed the trial. Two patients were withdrawn; one as a result of side-effects which were found to be associated with the placebo and one because of irregular attendance.

Although there was a strict random allocation of patients to groups 1 and 2. these two groups were not comparable during the control period. Those who were given the placebo before the indomethacin were more severely affected by rheumatoid arthritis than were those who were treated with indomethacin first and given the placebo subsequently.

The score by the systematic index of group 1 was 55 during the control period and for group 2 was 71, a difference of 16 units. This difference persisted throughout the trial, so that at the end of it group 1 had a mean systematic index of 44 units and group 2 of 57 units. Fortunately, there was a full range of all grades of patients in both groups; in group 1 the range of scores for the systematic index during the control period was from 73 units to 19 and in group 2 from 117 to 18.

A similar difference between these two groups could be shown for each of the indices used as a measure of disease for all indices except one, group 2 was more severely affected than group 1 during the control period and remained so throughout the trial period.

Articular index

A change of 10 or more in the articular index at the completion of the trial compared with the admission figure was taken to indicate either spread or regression of the arthritis.

Of the 28 patients 11 had a smaller index on completion, in nine it increased, and in eight there was no change. The timing of active therapy did not appear to affect this result. Of the 14 patients who received indomethacin in the last month one showed no change, six were worse, and seven better, as judged by the articular index.

1. Hand articular index

This is a measure of the patients' response to pain as well as the extent of the pain experienced. Both groups of patients showed a reduction of sensitivity to squeezing of finger joints during the course of the trial, and the rate of regression in the response to this procedure was the same for both groups irrespective of whether they were on the drug or on the placebo.

During the month on placebo the average number of painful joints for all patients was 9.2, whereas during the month on indomethacin the average was 9.5 joints affected, a completely negligible difference (see Statistical Tables). The number of patients who were better during the month on placebo was 15; 12 were better during the month on indomethacin and one was unchanged.

There was no evidence of any "carry-over" effect during the first two weeks after the use of indomethacin, nor was there any evidence of deterioration during the period on the placebo.

2. Pool of finger swelling

The use of jewellers' ring-gauges helped to eliminate the subjective response; none the less, there was a marked improvement in both groups of patients over the period. This may have been due partly to increasing patient-tolerance to the rings and partly ot the physician's increase in pressure when applying the rings.

Both groups responded in the same way on indomethacin. Group 1 improved slightly during the month and then continued to improve when placed on the placebo, and group 2 responded slightly on the placebo but continued to respond when treated with the active principle. Fifteen patients did better during the month on the placebo, whereas 13 did better on the indomethacin. The net result was that the mean score for both groups was identical at 366 units per patient. None of these differences are of formal statistical significance (see Statistical Tables).

Patients were selected for the presence of inflammatory finger-joint swellings. As some of these swellings were too large for measurement by the standard range of jewelers' ring-gauges, they were recorded as "53." Consequently, it was not possible to record fluctuations in their size. Accordingly, this factor would tend to reduce the amount of shift recorded in the pool of finger swelling. This point was examined by taking the six patients with a pool of finger swelling of "500" or over and comparing them as a group with the remaining 22 patients.

It was confirmed that though the contraction of the pool of swelling was less marked and the rate of improvement less steep in the group with the larger swellings the overall trend of this and the other measurements did not differ. Accordingly, this factor did not significantly affect the results.

3. Systemic index

(i) *Analgesic Tablets.*—Group 1 showed a decline during the period of treatment with a relapse when this was changed to a placebo, whereas there was no difference at all in the habits of group 2, who were rather more severely affected by the disease and were using more tablets. The mean difference between the two periods was negligible (see Statistical Tables). Fifteen patients took more tablets during the treatment period and 11 more during the placebo period; two remained unchanged.

(ii) *Duration of Morning Stiffness.*—This showed no consistent trends. Ten patients felt that they had improved during the treatment and 10 during the placebo period. Eight were the same during both months (see Statistical Tables).

(iii) *Fatigue.*—The delay in onset of fatigue suggests that indomethacin has some important "tonic" effect, but it is interesting to note that in this test alone group 1 was worse than group 2 during the control period. Group 1 rapidly improved on indomethacin and relapsed again on placebo, whereas group 2 grew worse on the placebo and improved on the drug. The overall effect was that the mean delay in fatigue was 5.9 hours on indomethacin and 5.1 hours on the placebo; this difference is not statistically significant (see Statistical Tables). Thirteen patients thought they were less fatigued during the treatment month and seven during the placebo month; eight detected no difference.

(iv) *Hand Grip.*—The ability to squeeze the bag improved with practice, and once again there was evidence of a "learning" effect in the changes. Group 1 was consistently better than group 2, but group 1 improved rapidly on indomethacin but failed to continue this improvement on placebo, whereas group 2 improved on the placebo and continued to improve on the drug. The net result was that the mean grip during indomethacin was 189 mm. Hg. and during the month on placebo was 185, a difference of 4 mm. Hg to the advantage of indomethacin (see Statistical Tables). Sixteen patients were better during the period on indomethacin and 12 during the placebo period.

(v) *Erythrocyte Sedimentation Rate.*—The E.S.R. is the only measurable variable that is not influenced by subjective feeling or observer error. The two groups were initially quite different from each other; group 1 had an E.S.R. of 55 mm. and group 2 of 71 mm., a difference of 16 mm. When group 1 was started on the drug there was an increase in the E.S.R., and when the placebo replaced it there was a sharp fall. Similarly, group 2 improved while on the placebo, but as soon as the drug was used the E.S.R. increased once again to a level higher than that during the control period. During the treatment period the mean rate was 48.6 mm. and during the placebo period it was 42.4 mm., a difference of 6.2 mm., with a standard error of 3.8 (t=1.8 P=0.1). Though the difference does not reach a formal statistical significance, the consistency of the pattern suggests that in fact indomethacin has an action to increase the E.S.R. (see Statistical Tables). Seven patients improved during the month on indomethacin and 21 during the month on placebo.

The *Systemic Index* is arrived at from aggregation of the results of the above five methods of measurement. It is already clear that there were no important differences. However, the systemic index was much higher in group 2 than in group 1, but both groups of patients improved steadily during the period of the trial. The mean score of the 28 patients during their month of treatment was 54.4 and during the month on placebo was 55.7, a difference of 1.3±4.0—a difference which is not statistically significant (see Statistical Tables). Sixteen patients were better during the treatment month, 11 during the placebo month, and one was unchanged.

4. Subjective opinion

Almost all patients felt that they had benefited by the treatment during the period of the trial, 13 throught they were better during the month on indomethacin, 13 preferred the month on placebo, and two were unable to distinguish the two periods (Fig. 2).

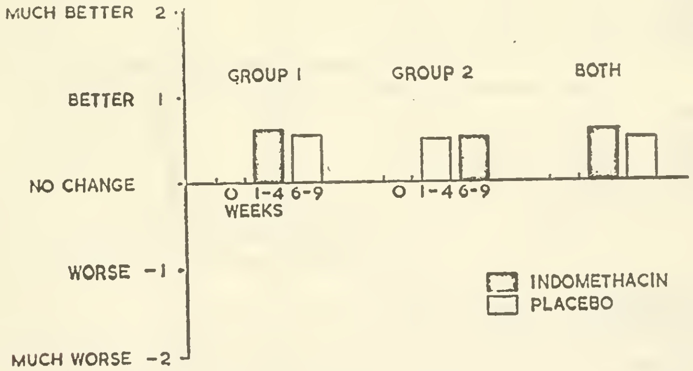

FIG. 2.—SUBJECTIVE OPINION.

TABLE I

Functional grade	Entering trial					
	I	II	III	IV	V	Total
Leaving trial:						
I	17	1	0	0	0	18
II	0	2	3	0	0	5
III	1	0	3	0	0	4
IV	0	0	0	1	0	1
V	0	0	0	0	0	0
Total	18	3	6	1	0	28

5. Functional grade

There were no significant differences here, and the results are set out in Table I. The inclusion of patients with long-standing disease did not affect the results; extraction of these results and comparison with the remaining patients and with those having disease of short duration showed no difference.

All the results have been reported as an average of four examinations during the month on indomethacin compared with a similar average while on a placebo. No substantial difference to any of the conclusions was made when the results for the fourth examinations alone at the end of each four-week period were compared with each other. The trends of the various responses during these two periods appeared to be similar, and hence should be attributed to some cause other than specific drug action.

SIDE-EFFECTS

The commonest side-effects were headache and gastro-intestinal upset. Though the incidence was equal for both indomethacin and placebo, the frequency was higher with indomethacin.

Side-effects occurred in 18 (60%) of the 30 patients while taking indomethacin and in 17 (56.7%) while taking placebo. In 9 (30%) patients side-effects were reported with both placebo and indomethacin, in 10 (33.3%) when taking placebo only, and in 11 (36.6%) with indomethacin alone. These are itemized in Table II.

TABLE II—SIDE-EFFECTS

Type of side effect	Patients affected		Weeks affected	
	Indomethacin	Placebo	Indomethacin	Placebo
C.N.S.	13	14	20	16
Headache	8	8	15	8
Sleepiness	3	1	3	3
Depression	1	2	1	2
Giddiness	1	2	1	2
Muzzy head	0	1	0	1
G.I.T.	16	12	25	14
Dyspepsia	5 }	3 }	6 }	4 }
Nausea	3 }	5 }	10 }	5 }
Anorexia	1 }12	1 }12	1 }20	2 }14
Vomiting	3 }	3 }	3 }	3 }
Diarrhoca	2	0	3	0
Activation of D.U.	1	0	1	0
Activation of hiatus hernia	1	0	1	0
Miscellaneous	10	8	12	11
Rash	2	1	3	2
Increase of arthralgia	2	1	3	2
Neck stiffness	1	2	1	2
Thrombophlebitis	1	1	1	1
Stroke	1	0	1	0
Fatigue	1	0	1	0
Scleral injection	1	0	1	0
Faint feelings	0	1	0	1
Excess sweating	0	1	0	2
Muscle weakness	1	1	1	1

One patient in group 2 withdrew from the trial because of severe side-effects which occurred during the first week of placebo administration. One man with doudenal ulcer and one woman with hiatus hernia, both diagnosed radiologically before the trial, experienced recurrence and worsening of dyspeptic symptoms while on indomethacin.

The occurrence of thrombophlebitis in one man on indomethacin was matched by a similar occurrence in one woman receiving placebo. Both had a previous history of thrombophlebitic episodes.

Transient loss of power in one arm was reported by a man with hypertension after receving indomethacin 50 mg./day for two days. Rapid improvement occurred and no further episodes were observed, though indomethacin was continued. Cerebral vascular accidents have been recorded previously in patients on indomethacin (Coste *et al.*, 1964).

STATISTICAL TABLES

Mean Scores and Standard Error of Mean.—The mean scores during the control period were based on one reading from each patient, and the mean scores during the treatment and placebo periods were based on four readings from each point.

The difference is taken in every case, so that, a plus sign indicates that the patients were better on indomethacin, a negative sign that they were better on placebo. Group 1: 14 patients treated with indomethacin followed by placebo. Group 2: 14 patients treated with placebo followed by indomethacin.

HAND ARTICULAR INDEX. NUMBER OF JOINTS PAINFUL

Group	Control period	Indomethacin	Placebo	Difference
Group 1	11·9	9·6±0·9	7·6±0·9	−2·0±1·3
Group 2	12·7	9·4±0·8	10·7±0·8	+1·3±1·1
All patients	12·3	9·5±0·6	9·2±0·6	−0·3±0·9

POOL OF FINGER SWELLING. SUM OF JEWELERS' RING-GAGES PASSED OVER THE FINGER

Group 1	374	366±10	349±10	−17±14
Group 2	388	366±10	383±10	+17±14
All patients	381	366±7	366±7	0±10

USE OF ANALGESIC TABLETS. NUMBER OF TABLETS USED DAILY TO RELIEVE PAIN

Group 1	5·9	4·3±0·5	4·8±0·5	+0·5±0·7
Group 2	7·5	7·5±0·7	7·6±0·8	+0·1±1·6
All patients	6·7	5·9±0·4	6·2±0·5	+0·3±0·0

MORNING STIFFNESS. DURATION IN HOURS UNTIL STIFFNESS RELIEVED

Group 1	1·9	1·9±0·35	2·0±0·43	+0·1±0·56
Group 2	2·0	2·0±0·34	2·0±0·23	0·0±0·41
All patients	1·9	2·0±0·24	2·0±0·24	0·0±0·35

DURATION OF FATIGUE. HOURS UNTIL ONSET OF FATIGUE

Group 1	4.5	6·0±0·6	5·2±0·6	+0·8±0·8
Group 2	5·9	5·8±0·6	4·9±0·5	+0·9±0·8
All patients	5·2	5·9±0·4	5·1±0·4	+0·8±0·6

N.B.: An increase in this score means the patient has improved.

HAND GRIP. PRESSURE (MM. HG) IN SPHYGMOMANOMETER BULB[1]

Group 1	164	196±9·5	195±9·1	+1±13
Group 2	153	183±10·4	176±9·3	+7±14
All patients	158	189±7·1	185±6·5	+4±10

ERYTHROCYTE SEDIMENTATION RATE. MILLIMETERS (WESTERGREN)

Group 1	44·7	46·1±4·0	39·5±3·7	−6·6±5·5
Group 2	49·1	51·0±3·3	45·3±3·6	−5·7±5·1
All patients	46·9	48·6±2·7	42·4±2·6	−6·2±3·7

SYSTEMIC INDEX. UNITS

Group 1	55	48·9±3·0	48·2±3·8	−0·7±4·8
Group 2	71	59·8±4·2	63·2±4·7	+3·4±6·3
All patients	63	54·4±2·6	55·7±3·0	+1·3±4·0

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[1] An increase in this score means the patient has improved.

DISCUSSION

This trial differs in three important respects from all trials previously reported. Two of these concern modifications to the standard double-blind crossover techniques.

1. The placebo effect that often occurs early during the administration of any drug was diminished by the addition of a pretrial week of placebo only. As a result of the baseline figures obtained at entry and used for subsequent comparison, though smaller, were more accurate.

2. Another week of placebo administration was inserted at the crossover in order to minimize dilution of measurements, early in the placebo month, by carry-over of drug response in those patients receiving the drug first.

3. The incremental dose schedule was fixed, and remained unaltered despite the occurrence of side-effects and apparent therapeutic response.

In many of the previously reported trials the dose of indomethacin was permissive, depending on the above factors, with consequent variation in the maximum daily dose achieved in the individual patient, varying from 75 to 300 mg.

In a somewhat similar trial Ward (1964), using indomethacin 200 mg./day in tablet form, demonstrated improvement in morning stiffness and joint tenderness but no change in finger swelling (measured by ring size), grip strength, or in the patient's assessment of pain. In a subsequent double-blind (but *not* crossover) trial, using 150 mg./day in capsule form, he confirmed the above findings except that pain was lessened, and an additional measurement of swelling of larger joints (estimated by eye) was said to show improvement by indomethacin. Thus his claim for beneficial effects was based on subjective measurements only.

Within the dose and time limitations of our trial there was no indication of any anti-inflammatory, detumescent, or analgesic effect of indomethacin on patients with rhuematoid arthritis that could be detected statistically by the eight criteria used.

Two measurements remained unchanged throughout the 10 weeks of the trial—duration of morning stiffness and patients' opinion. Four others showed changes that could not be regarded as significant.

Only two of the criteria used were affected by indomethacin—E.S.R. and time to onset of fatigue—through the changes demonstrated did not reach the level of formal statistical validity.

The delay in onset of fatigue, without other evidence of improvement, was quite noticeable. Many of the patients reported considerable increase in the amount of physical activity they were able to undertake. This effect of indomethacin has not been previously reported. The rise in E.S.R. has been reported—Miehike (1965) found an increase in 21 out of 53 rheumatoid patients who were on indomethacin, and Rubens-Duval and Villaumey (1964) reported raised E.S.R. in some patients. Persistence of an already elevated E.S.R. despite clinical improvement has been noted by Viara and Marrazzi (1964), Katz *et al.* (1965), and Robecchi *et al.* (1964). The mechanism of this E.S.R. rise is obscure and is being investigated.

An important practical point emerges: in patients with rheumatoid arthritis receiving indomethacin it would seem that the E.S.R. can no longer be regarded as a reliable indicator of disease activity.

The two most important clinical indicators of inflammation used in this trial were the hand index and pool of finger-joint swelling. Both of these showed systematic improvement throughout the course of the trial, suggesting that the factors influencing these changes were the results of learning and placebo rather than the expression of any pharmacological effect that could be attributed to indomethacin. These improvements were not the result of changes to be expected in some patients attending for the first time after a recent onset or exacerbation of arthritic disease. All patients, with one exception, were selected from the regular panel of the follow-up clinic, from patients with fixed review appointments. This general placebo response was borne out by the patients' opinion of the effect of the capsule; 24 of the 28 patients completing the trial elected to continue taking indomethacin capsules even though only 14 were actually receiving the drug at the time of their decision.

There was no evidence of any decrease in joint pain within two to three days, but we did conform the measurable reduction in finger-joint swelling reported by Hart and Boardman (1963) with doses varying from 50 to 150 mg.; we have demonstrated that this is a learning effect. Katz *et al.* (1963) noted a therapeutic response within 24 to 48 hours, and Ballabio *et al.* (1963), administering doses of indomethacin as low as 100 mg./day, claimed to show anti-inflammatory effects in rheumatoid arthritis within a few hours of administration. We failed to conform this. Neither did we find evidence of the rebound exacerabation associated with suddent cessation of indomethacin treatment experienced by other workers (Katz *et al.*, 1965).

The use of an "all-or-none" response to digital pressure applied by the assessor as an indication of joint tenderness was thought to be a more accurate measurement for assessing inflammation at weekly intervals than grading the response. It was thought that, even with the same physician taking the measurements, it was impossible to apply the same pressure at weekly intervals with sufficient accuracy to make grading of any value.

We failed to show any analgesic effect of indomethacin, as judged by a fall in the number of analgesic tablets taken each day. The apparent beneficial effect demonstrated in group 1 was offset by the lack of response in group 2, who had the more severe disease. No conclusion can be made from these results. Despite repeated instruction that analgesic tablet dose was to be related to the degree of arthralgia some patients were reluctant "to take tablets." Others, particularly those in group 2, were disinclined to alter a long-established rigid dose-scheme of analgesic tablets. On the other hand, incidental discomfort, not related to the arthritis, as with coryza, influenza, headaches, and even side-effects of the drug, affected the number of aspirin tablets taken by those who carried out their instructions precisely. Of all the measurements used it was thought that this was the least reliable.

With adequate time spent on explanation and rehearsal, our method of measurement of grip strength was accurate enough to justify its substitution for the more time-consuming method suggested by Lansbury (1958). A pretrial comparison of these two methods showed very little difference.

The patients' opinion of the effectiveness of the capsules was found to be a subjective and unreliable indicator on which to base a judgement. In addition to the "normal" clinical variation in feeling of well-being and mood, the incidence and type of side-effects associated with the use of the capsules obviously influenced the patients' opinion. It was also found that the expressions "worse" or "much worse" could apply to the day of assessment or to the previous day, rather than to the week as a whole; the patients memory of their feelings over the previous week tended to be influenced by their immediate feelings on the day of examination.

The systemic index of patients receiving indomethacin would have shown improvement on this trial were it not for the rise in E.S.R. On the other hand, any fall in the index would then have been due entirely to the effect of the indomethacin in delaying the onset of fatigue; for the other three measurements—grip strength, dose of analgesic tablets, and duration of morning stiffness—remained unaffected.

We took great care to avoid suggesting side-effects to our patients, but in spite of this symptoms occurred with approximately equal incidence during drug and placebo administration and followed a similar pattern in both groups. However, the frequency was greater with indomethacin, notably as regards headache and gastrointestinal upset. It is worthy of note that the only patient withdrawing from the trial developed headache, nausea, anorexia, and skin rash after receiving only placebo for four weeks. This picture indicates that suggestion did in fact play a large part in producing side-effects. We could not eliminate cross-chat in the waiting-room between patients in the trial and also between other patients taking indomethacin outside the trial.

A high placebo response is a well-recognized feature in patients attending a rheumatological clinic, and the high level of placebo response implies susceptibility to other forms of suggestion; our results support this. This seems to indicate that the true incidence of side-effects attributable to the drug is very much less than the 50 to 70% recorded here and in other papers. We regard the 37% of patients who developed side-effects on indomethacin alone as a more realistic estimate, but even this figure may be an exaggeration, for 30% experienced similar side-effects while receiving placebo.

SUMMARY

In a double-blind crossover clinical trial occupying 10 weeks indomethacin was given in capsule form for four consecutive weeks, starting with a daily dose of 50 mg. and increasing by one 25-mg. capsule a week to a maximum of 125 mg./day. The results on 30 patients with classical or definite rheumatoid arthritis are tabulated and discussed.

With the criteria of assessment based on the systemic index and articular index of Lansbury and measuring finger-joint swelling by means of jewellers' ring-gauges it was not possible to show that indomethacin produced any antiphlogistic effect that held statistical validity. The detumescent and analgesic effects demonstrated were shown to be the result of placebo and learning factors.

A tendency for indomethacin to accelerate the rate of erythrocyte sedimentation was revealed, and evidence for a specific anti-fatigue effect of the drug in rheumatoid arthritic patients is presented.

Side-effects are listed. Though they occurred more often with indomethacin, the incidence, type, and pattern were the same with both drug and placebo. The inference is made that suggestion played a part in determining both the incidence and the variety of side-effects encountered in the trial.

Compilation of our findings was considerably assisted by computer analysis of the figures; our thanks are due to Messrs. Merck Sharp and Dohme Ltd. for a grant to defray the expenses of this, also to Dr. Robert Hodgkinson, of the same firm, for his advice, for supplying the placebo and indomethacin capsules, and for arranging the randomization.

Our thanks are also due to the staff of the pathology and pharmacy departments of the Cardiff Royal Infirmary; to our secretaries and the medical illustrators who were so helpful; and to Nurse Jenkins, of our outpatient department, who assisted in the weekly clinics.

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(Whereupon, at 10:35 a.m., the hearing was recessed, to reconvene Wednesday, May 1, 1968.)

COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

WEDNESDAY, MAY 1, 1968

U.S. Senate,
Monopoly Subcommittee of the
Select Committee on Small Business,
Washington, D.C.

The subcommittee met, pursuant to recess, at 10:05 a.m., in room G308, New Senate Office Building, Senator Gaylord P. Nelson (chairman of the subcommittee) presiding.

Present: Senator Nelson.

Also present: Benjamin Gordon, staff economist; James H. Grossman, minority counsel; Susan H. Hewman, research assistant; Elaine C. Dye, research assistant; and William B. Cherkasky, legislative director, staff of Senator Nelson.

Senator Nelson. We will open the subcommittee hearings this morning.

We have with us from the Food and Drug Administration Dr. Robert Hodges, Dr. John Jennings, and Dr. Marion Finkel. The opening testimony will be by Dr. Hodges.

Do you have a biographical summary to submit for the record?

Dr. Hodges. Yes, sir. It is attached to my testimony.

Senator Nelson. It will be printed in full in the record.

(The biographical summary follows:)

Curriculum Vitae—Robert Manley Hodges, B.Sc., M.B., B.Ch., D.R.C.O.G., F.A.C.O.G.

Personal data

Citizenship: U.S.A.—Naturalized, Alexandria, Va., April 4, 1964. Certificate #8690576.

Birth: July 13, 1924. Llandrindod, U.K.

Home Address: 311 S. Pitt St., Alexandria, Va.

Marital Status: Married in 1957; 4 children.

Education

B.Sc.: University of Wales, July 1950.

M.B., B.Ch.: University of Wales, July 1953.

House Physician: East Glamorgan Hospital, U.K., July 1, 1953 to January 1, 1954.

House Surgeon: Royal Infirmary, Cardiff, U.K., January 1, 1954 to July 1, 1954.

House Surgeon in Obstetrics: Royal Infirmary, Cardiff, U.K., August 1954 to February 1955.

Assistant Resident: Pathology, Ottawa General Hospital, Ottawa, Canada, June 30, 1956 to June 30, 1957.

Assistant Resident: Obstetrics and Gynecology, Boston City Hospital, Boston, Mass., July 1, 1957 to July 1, 1958.

Resident, Chief Resident: Obstetrics and Gynecology, King County Hospital, Seattle, Wash., July 1, 1958 to January 1, 1960.

Military service

April 1943 to July 1947, British Army.

Teaching appointments

Demonstrator in Pathology, University of Ottawa, Canada, June 1956 to June 1957.

Instructor in Obstetrics and Gynecology, University of Washington, Seattle, Washington, July 1959 to July 1961.

Clinical Associate in Obstetrics and Gynecology, University of Washington, Seattle, Washington, 1961–1963.

Hospital appointments

Attending Staff, King County Hospital, Seattle, Washington, January 1960–1963.

Attending Staff, University Hospital, Seattle, Washington, July 1960–1962.

Attending Staff, Alexandria Hospital, Alexandria, Va., 1964 to present.

Current activity

Bureau of Medicine, Food and Drug Administration—Medical Officer, July 1, 1963 to July 10, 1966; Director, Officer of New Drugs, July 11, 1966 to present (Acting Director to May 7, 1967).

Medical licensure

United Kingdom 1954; Canada 1955; Washington State 1960; Virginia 1963 #16440.

Postgraduate qualifications

Diploma of Royal College of Obstetricians and Gynecologists, 1955.

American Board of Obstetricians and Gynecologists, 1967.

Professional organizations

Fellow, American College of Obstetrics and Gynecology.

Alberta College of Physicians and Surgeons 1955–1956.

King County Medical Society 1961–1963.

Alexandria Medical Society.

American Society for Pharmacology and Experimental Therapeutics (pending).

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Senator NELSON. You may proceed to present your statement in any way you see fit. I assume you have no objection to interruptions for questions.

Dr. HODGES. Of course not.

Senator NELSON Please go ahead, Doctor.

STATEMENT OF DR. ROBERT M. HODGES, DIRECTOR, OFFICE OF NEW DRUGS, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. MARION FINKEL, OFFICE OF NEW DRUGS, FDA; AND WILLIAM W. GOODRICH, GENERAL COUNSEL, FDA

Dr. HODGES. Mr. Chairman, I appreciate this opportunity of appearing before you this morning to discuss the approval of the New Drug Application for Indocin, Merck Sharp & Dohme's brand name for indomethacin.

The statement I have is a long one, Mr. Chairman, and at some places I will abbreviate it, unless you wish me to read it in full.

Senator NELSON. No. We will print your statement in full. And if you wish to condense it or extemporize in any way you may do so.[1]

Dr. HODGES. As the name of my office implies, the Office of New Drugs, which is under my direction, reviews all Investigational and New Drug Applications for drugs prior of their introduction to the market.

Clinical trials with indomethacin were underway at the time of the new requirements of the Kefauver-Harris Drug Amendments and the investigational new drug regulations became effective in 1962. Many of the early studies and much of the clinical data in the New Drug Application thus reflect a different kind of clinical investigation than that required under the 1963 regulations.

Senator NELSON. For the record, will you state what was required prior to the 1963 regulations?

Dr. HODGES. Prior to the 1963 regulations there was no requirement that efficacy be demonstrated, and no requirement that an investigational new drug notice be submitted to the Food and Drug Administration before clinical studies could proceed. This meant that we had no knowledge of studies that were going on with investigational drugs. We were not able to contribute any comments to the drug studies prior to the time that we received the New Drug Application.

Senator NELSON. The procedure, then, was that a company experimenting with a new drug could do trials on animals, for example, and then proceed to trials on humans, without an IND notice being required.

Dr. HODGES. The only requirement was that the drug had to be labeled "For clinical investigation only."

Senator NELSON. Now, since 1963, at the stage when a company desires to experiment on human beings, they have to make an application and get FDA approval in advance, is that correct?

Dr. HODGES. No, they don't have to have approval in advance. They have to submit to us an investigational new drug notice which will contain enough data for us to be able to determine that it is safe and reasonable to do what they proceed to do on human beings.

As soon as the application has been submitted to us, they are then free to proceed with the trials without requiring any authorization or permission from the Food and Drug Administration, that is, with the exception of a very few named drugs such as DMSO (dimethylsulfoxide) which we consider to be sufficiently toxic that we require preclearance for studies. We can, of course, terminate the study as soon as we wish if we feel that it is not safe for the study to proceed. This can be done, and has in a few instances, within a few weeks of receiving the notice that the applicant is about to start the studies. And this in effect means that the studies never get going.

Senator NELSON. So they submit the IND with their experimental animal data, and then proceed. If in review of that data you decide they should not proceed, you have the authority to stop the experiment at that stage?

Dr. HODGES. That is right.

Senator NELSON. As a matter of practice within the Food and Drug Administration, how long does it take to review an IND and make a decision that it is all right to proceed, or a decision that they should not proceed?

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[1] The complete prepared statement submitted by Dr. Hodges begins at p. 2919, infra.

Dr. HODGES. At present we attempt to review all IND's completely (clinical controls, pharmacology and clinical data), by the three professional reviewers, within 60 days of the receipt of the notice. This is the general rule. If a drug appears to be toxic, or if we have some reason to be concerned with it, we accelerate this. We have completed our reviews and proposed the action that seemed appropriate to the Commissioner within 10 days of receipt.

Senator NELSON. You say 60 days is the general rule. What in fact is the practice? What percentage of the cases do you complete within the 60-day period?

Dr. HODGES. We have at present some 4,600 investigational new drug notices, of which about 2,400 are active. In other words, there are studies going on with those 2,400, and all except about 300 have had their total review.

Senator NELSON. Within a 60-day period.

Dr. HODGES. Within a 60-day period.

Senator NELSON. How many IND's do you get a year?

Dr. HODGES. Between 600 and 700.

Senator NELSON. What was the 2,000 figure you were referring to?

Dr. HODGES. Of the applications that were submitted 2,600 are still active. The remainder——

Senator NELSON. You mean these drugs are under investigation and experimentation now?

Dr. HODGES. Now. Of the remaining 2,200, the experiments either have been completed or were never started, and the notices have been discontinued, or we have terminated them because of lack of safety.

Mr. GORDON. How many people do you have working on these?

Dr. HODGES. The strength of the Office should be about 220 to 230. In fact, we have as of today about 170 people in the Office of New Drugs. The working time is divided roughly in half between a review of investigational new drug notices and a review of New Drug Applications for marketing.

Senator NELSON. And in that section of the Food and Drug Administration what are the professional credentials of the people? What is the breakdown of their credentials?

Dr. HODGES. We have three main classes of professional reviewers: chemists, pharmacologists, and M.D.'s. In my office all of the M.D.'s are board eligible—almost all; I would have to review each one in detail to say all—almost all are board eligible, or actually have their board qualifications in a medical speciality. Of the pharmacologists, a number have a Ph. D. in pharmacology, others have a master's degree in pharmacology, and others have a bachelor's degree in pharmacology.

In chemistry we have similar qualifications—some Ph. D.'s in chemistry, some masters of science, and some bachelors of science.

In addition, of course, we have a clerical staff and a number of Food and Drug officers and pharmacists who provide support and assistance.

Mr. GROSSMAN. Doctor, am I correct in assuming that there are 170 on your staff to deal with something like 4,000 of these applications within 60 days; is that about right?

Dr. HODGES. Not at one time. We don't have 4,600 active IND's at the moment. Two thousand two hundred have been processed completely, and are now inactive.

Mr. GROSSMAN. At any one time, is what I am trying to get; at any one time how many of these applications are these 170 working on?

Dr. HODGES. 2,400 investigational new drug notices.

Mr. GROSSMAN. Do you feel that this allows them sufficient time to make an independent judgment on this?

Dr. HODGES. I think that we are just about at the point where we can do it with the staff that we now have. But the full-time evaluation of investigational new drug notices, and New Drug Applications limits the time that we can spend on other aspects, such as further professional development and consultation. Our office renders a considerable service in providing consultations for other offices of the Bureau of Medicine, and other bureaus of the Food and Drug Administration.

Mr. GROSSMAN. In essence, though, this is their only main responsibility?

Dr. HODGES. Our main responsibility; yes.

Mr. GROSSMAN. Thank you.

Senator NELSON. If I understood you correctly, you average about, did you say, 600 new IND's a year?

Dr. HODGES. That is right, 600 new ones are received. About 450 of those that were active become inactive—the studies are completed, or not started or we stop them. So each year we have a net increase of 150 to 200 new IND's that become active or stay active.

Senator NELSON. But these 2,400, that is an accumulation, the average over a 4- or 5-year period?

Dr. HODGES. That is correct.

Senator NELSON. And the experiments are going on. And you did approve those applications, most of them, within a 60-day period, at the time the IND was filed?

Dr. HODGES. Yes. But by implication we have granted approval, in that we have not taken any action to order the studies to be discontinued. However, in a great many of these we will have written to the firms and made them suggestions either improving the design of the studies from the point of view of efficacy, or from the point of view of safety—more the latter. Our main concern in the investigational stage has been in the past, and I think must continue to be, with the safety of the study and the individual patient involved in the study.

Senator NELSON. But of that 2,400, each of them was in due course reviewed, most of them within the 60-day period, and a decision was made not to stop the experimentation; is that correct?

Dr. HODGES. That is correct.

On May 3, 1963, the IND for indomethacin was submitted by Merck Sharp & Dohme. It showed that the investigation was in phase 3, clinical trials. This means that they had passed the stage of determining the safety, and the drug appeared to have some efficacy, so they were now in the stage of confirming the right dosage and the right indications.

Senator NELSON. For human use?

Dr. HODGES. For human use.

Senator NELSON. And this was prior to the effective date of the Kefauver-Harris Act?

Dr. HODGES. That is right.

Senator NELSON. So at that stage they didn't need an IND to start?

Dr. HODGES. No. These studies were underway at the time the act became effective. So they were required to submit the notice. The first study was already well in progress.

Mr. GOODRICH. May I comment on this. When the Kefauver-Harris amendments became effective in October of 1962, when they were passed they had a lagtime, and we had already proposed adoption of the investigational new drug regulations. They were adopted about the first of the year. And for all investigations underway on August 10, 1962, when the regulations were first announced, it was required that the plan be submitted by June 5, 1963. Merck Sharp & Dohme came in in May of 1963 with a large number of IND's for ongoing studies on that date.

Dr. HODGES. The preclinical data were adequate and the clinical trials were being conducted by a number of well-qualified rheumatologists. A year later, on June 5, 1964, the New Drug Application was submitted. In accordance with our regulations, the firm was required to submit the names of all investigators who had received the drug, along with the results of all investigations, or an explanation if any were omitted.

The New Drug Application was a voluminous document. It was submitted for use of the drug in rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis—generalized and of the hip—gout, acute bursitis, synovitis, tenosynovitis and tendinitis.

There were extensive studies and review of the application and in January 1965 it was ruled incomplete; that is, nonapprovable, until further data were submitted and until clarification of possible adverse effects on kidney function had been elucidated. The package insert was considered inadequate in that it did not present a true picture of the contraindications, warnings, precautions, adverse effects, toxicity, and in that it did not exclude the use of the drug in children. In addition, the firm's discussion of the clinical studies in the insert was not balanced; too much weight was given to favorable results.

The following changes in the proposed package insert were recommended in a letter to the company on January 13, 1965——

Mr. GORDON. When you received this material at the FDA what did you do with it? Did you perform any investigations on your own, or did you accept what the firm gave you? What is the procedure?

Dr. HODGES. With any application—and this would apply to this one—the material that is submitted goes through our procedures for filing and documenting and giving numbers, and then it is sent to one of six specialty divisions within the Office of New Drugs. Then it is reviewed within that division by a chemist, a pharmacologist, and a medical officer. This review is only a review of the data submitted. We do not do any studies ourselves on an original New Drug Application.

When we have completed our review, or sometimes during the course of the review, we may obtain consultation with outside experts, or within the Bureau itself. We make our judgment on the data that is submitted by the firm.

Mr. GORDON. So to a considerable extent you are dependent on what the firm gives you?

Dr. HODGES. Almost 100 percent in most instances.

Mr. GORDON. Now, you talk about how much weight was given to favorable results, and you also talk about unfavorable results. Can you characterize in some way the weight given to the unfavorable results?

Dr. HODGES. The weight given to the unfavorable?

Mr. GORDON. Yes.

Dr. HODGES. Well, it was a lack of weight, in that we did not feel that they were sufficiently expressed in the package insert sent with the drug that will go to the physician.

Mr. GORDON. The firm proposes the package insert to you, is that the way it works?

Dr. HODGES. Yes. We approve all the labeling and all the printed material that accompanies the drug. The principal one as far as the doctor is concerned is the package insert.

Mr. GORDON. You don't write the package insert, the company writes it; is that correct?

Dr. HODGES. Well, after we have finished with it, it very often looks as though we have written it. But the company is supposed to write the package insert completely.

Senator NELSON. Do they submit the package insert for approval?

Dr. HODGES. Yes. We make our review based on that package insert, because we review the application in the light of the claims that they were making in the package insert.

Senator NELSON. Do you have the authority under the law to require them to delete any claims made and to require that certain statements be included?

Dr. HODGES. Yes. Since we approve the package insert, if they don't make the changes that we require we will not approve it. The applicant, if he disagrees with our finding, has the option of going to a higher authority on this. But they rarely elect to do this.

Senator NELSON. In your judgment, how effective so far as getting the warning, indications, and contraindications to the doctor is concerned, is the package insert? Does he see it, for example?

Dr. HODGES. I think that this is a question that is difficult to answer. We would like to think that the doctor sees the package insert, or at least a brochure which contains substantially the same material that is in the package insert on every drug that he prescribes. When I was in practice myself I did not use any drug that I had not been made very familiar with in medical school without reviewing all the data that was easily available to me. This usually meant the package insert or the brochure, which is based on the package insert, is sent to each physician.

Senator NELSON. The package is sent to each physician?

Dr. HODGES. No, a brochure made up from the package insert is sent to each physician. And if he receives samples of the drug he will receive a copy of the package insert with a drug sample. Since most physicians receive samples of new drugs, he will receive the package insert. Now, whether he reads it or not we can't say.

Senator NELSON. The brochure that you referred to, what is that?

Dr. HODGES. This is usually a booklet, it can be a small one, perhaps 4 by 5 inches, it can be a large booklet, as large as these sheets, and with glossy paper, or with some promotional aspect to it. But substantially it has to contain what is in the package insert in fair balance.

Senator NELSON. But the brochure itself is an advertisement?

Dr. HODGES. Well, I think it contains promotional material. But the intent is to inform the physician fully about this drug.

Senator NELSON. Does the FDA approve the brochure?

Dr. HODGES. We may. In the past we have usually had the brochure submitted to us at the same time as the package insert. More recently, most firms have stopped sending an actual brochure with the original NDA.

Senator NELSON. They have stopped sending the brochure?

Dr. HODGES. They don't send in the brochure with the original application. But if we subsequently find any material in the brochure that is false or misleading we will take action against them. They submit it as a supplemental application after approval.

Senator NELSON. But you approve the package insert, and therefore you approve the wording and the placement of the warning and all that. But I take it you don't do that respecting the brochure?

Dr. HODGES. If it is principally advertising material we don't give approval or preclearance to these materials.

Senator NELSON. Isn't it correct that for most of the drugs that the doctor prescribes he doesn't see the package insert, because the package goes directly to a prescription drug store, and the doctor never sees it, isn't that correct?

Dr. HODGES. That is correct. The package insert accompanies the actual drug. The actual drug that is prescribed the physician would not be expected to see. But as I mentioned earlier, samples are sent for almost all new drugs to physicians, as starter samples. These samples must contain a copy of the approved package insert.

Senator NELSON. So the doctor may or may not be sent a sample, and he may or may not use it?

Dr. HODGES. That is correct.

Senator NELSON. And then if, based upon some subsequent knowledge, the package insert is changed, how does the doctor keep up on that?

Dr. HODGES. The promotional material will reflect the changes in the labeling. If he receives any more samples after the change, the new sample must contain the revised package insert. If it is a significant change, the firm will also be required to send a "Dear Doctor" letter informing the physician of the change.

Senator NELSON. I understood that it was the conclusion of the FDA at some stage, I don't remember the date, that indomethacin should not be used in the treatment of children. When was that?

Dr. HODGES. We made that decision prior to approval. It was never approved for use in children at any time, although it was in our original labeling, that is, the package insert—may I read to you what we approved? The first package insert was approved. We stated in the contraindications (this is the strongest warning section that there is): "Since experience with indomethacin is limited, it is recommended that the drug should not be administered to pediatric groups until indications for use and dosage have been established."

Now, after marketing—it is not my place to deal with after marketing—but I would mention that it was found after the drug was marketed that apparently the drug was used in children. A "Dear Doctor" letter was sent to the physicians warning them against the use in children.

Senator NELSON. I have some questions on that point a little further on, but I think we will just wait.

Dr. HODGES. I think Dr. Jennings in his testimony will deal again with this matter, because he dealt with it in his office.

The following changes in the proposed package insert were recommended in a letter to the company on January 13, 1965:

Deletion of all claimed indications other than rheumatoid arthritis, rheumatoid spondylitis, and gout. (That is deletion of osteoarthritis, generalized and of the hip, acute bursitis, synovitis, tenosynovitis, and tendinitis.) (Later, osteoarthritis of the hip was permitted following submission of controlled studies.)

Senator NELSON. You did not permit them to include claims for osteoarthritis, acute bursitis, and so forth, because they did not submit sufficient evidence to indicate that the drug was efficacious for those conditions?

Dr. HODGES. That is right. The data submitted in the New Drug Application were not adequate to support the efficacy of the drug in this condition. We required modification of the claims under rheumatoid spondylitis. The proposed package insert stated that Indocin "usually" produces marked relief of pain and improved motion of the spine within 3 to 10 days "in most patients." We modified the "usually" to "frequently" and deleted "in most patients."

Modification of the claims under gout: The submitted insert stated that in acute gout, marked reduction of pain "is usually" obtained within 2 to 4 hours. We substituted the words "may be." Further, during a discussion of the interval phase of gout, it was stated that indomethacin plus a uricosuric agent "usually" provides relief of pain and prevents recurrence of acute attacks. We substituted "may provide."

Senator NELSON. Why did you decide to substitute these words?

Dr. HODGES. We felt that the claims were too dogmatic. They implied that relief occurred either more often or in more patients than the data appeared to indicate. We felt that by these changes we reflected more accurately what the data showed.

Senator NELSON. Your conclusion as to the use of the word was based upon the data they submitted to you?

Dr. HODGES. That is right, Senator.

We felt that the contraindications section was too brief and did not include a true picture of the toxic potential of the drug. We recommended that this section be revised and considerably expanded as follows:

"As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration. For these reasons it should not be given to patients with active peptic ulcer. Inasmuch as this drug may cause irritation of the gastrointestinal tract, it is also contraindicated in patients with gastritis, ulcerative colitis, and regional enteritis. Indocin is contraindicated in patients with renal disease, psychosis, or marked emotional instability, and central nervous system diseases such as epilepsy and parkinsonism. It is also contraindicated in patients with a history of blood dyscrasia."

Mr. GORDON. It seems to me that if a drug is contraindicated in a certain condition, it should never be used when that condition exists. Consequently, the language should be clearcut, in my judgment. Now, do you think that this—especially the first part—is clear and concise? For example, the words "As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration." Why don't you just say, "Where there are signs and symptoms of peptic ulcer it should not be used?" Isn't it possible that the style tends to water down the effect?

Dr. HODGES. I don't think so, Mr. Gordon. A patient who, for instance, did not have a previous history of peptic ulcer and was not known to have a peptic ulcer, could develop one while on the drug. And because of the masking effect of Indocin it could be missed. There could be perhaps some bleeding or some other sign that might not alert the physician to the presence of duodenal ulcer, or a gastric ulcer, because the patient was on indomethacin.

Senator NELSON. What is the interpretation of the FDA of the word "contraindication?"

Dr. HODGES. It means that under the conditions listed that we feel that the toxicity of the drug appears to outweigh the benefits that may be expected to be obtained. It is a relative term. And there are patients who perhaps have emotional instability, for instance, but whose rheumatoid arthritis is so severe that in spite of the counterindication in the labeling the physician may feel that, taking all factors into account, the drug should still be prescribed for this patient. This is his privilege.

Senator NELSON. Would there be patients who may have an active peptic ulcer and should still receive Indocin for rheumatoid arthritis?

Dr. HODGES. I would say that is close to an absolute indication, in other words, an absolute contraindication. It just should not be used. This is true for Indocin, and it is certainly true for the cardiosteroids. And it is just about absolute.

Senator NELSON. For the wording of the contraindication, where you say, for these reasons it should not be given to patients with active peptic ulcers, shouldn't it just say, "never be given?"

Dr. HODGES. I would feel as a physician, if I read this, I would feel it was pretty strong.

Senator NELSON. Your statement was pretty strong a moment ago.

Dr. HODGES. Yes, I agree. But——

Senator NELSON. You said that this should not be given, period.

Dr. HODGES. I would feel that is clear from the combination of this labeling plus the knowledge that every physician has, certainly should have, about other inflammatory agents—this is why this is brought in, to alert a physician to the fact that this drug can do exactly the same thing as the corticosteroids. This is something that is stressed in medical school, in medical school training and in postgraduate training. I would be surprised if there were many physicians in this country who were not aware of the danger of using cortisone, for instance, in a patient with a peptic ulcer, or a history of peptic ulcers. This puts the drug in the same class, and alerts the physician to the danger.

Senator NELSON. I guess we will get to that later on. But it appears to be the position of the FDA that physicians should never give it to children. And yet the evidence is that it is prescribed for children. And one of the doctors in the FDA says it may be as widely and badly misused as chloramphenicol.

Dr. HODGES. Well, we certainly felt that there was use in children, and required the "Dear Doctor" letter to bring this to the physicians' notice that this use was not approved.

Senator NELSON. What puzzles me in looking at the package inserts is that the insert plus the advertising, time after time, serves to mask the caution that the Food and Drug Administration says should be exercised. In the ads the firms mask it, in the package insert they mask it also. It seems to me that if you have positive information you should state it clearly and in boldface type.

Dr. HODGES. There are a few absolute contraindications. But most of them, as I have indicated, are relative, and there are only a few instances where we can come out flatly and say, this drug should never be given to such and such a type of patient.

Senator NELSON. Can you think of any case of active peptic ulcer where you would still use it for rheumatoid arthritis? I cannot, can you?

Dr. FINKEL. Well, as Dr. Hodges pointed out, most of the contraindications are, in a sense, relative. The physician has to use his judgment at times if there is nothing else available. I am not referring to this drug, but just in general, despite the fact that there is a contraindication. As an example, tuberculosis. When a patient with tuberculosis receives cortisone it can spread the disease quite markedly. But on the other hand if the patient has, in addition, another disease which is life-threatening, and the only thing that can be used is cortisone, then the physician must use cortisone.

There are some cases where the physician has to use his judgment.

Mr. GORDON. What about peptic ulcer?

Dr. FINKEL. As it happened, in the investigational phase there were some patients with active peptic ulcer who received indomethacin. The ulcer had preceded the use of indomethacin, they had gotten it while they were on cortisone. And the ulcer healed. Nevertheless, we felt that we should strongly state that it should not be given, because we really feel that way. But it is possible that in certain instances, if there was nothing else available, the drug would have to be used.

Senator NELSON. Then why shouldn't you say it should not be used and go on further to say that there may be instances where it would be necessary, and you would advise the doctor, if he is not an expert himself, to consult somebody else as to these indications? In other words, if it was a rare, rare case, why leave the wording so that it can be misinterpreted?

Dr. HODGES. We felt that as this label was written and as we had approved it, that the physician could get this inference. As I have indicated, I would be disinclined—I don't think I would use it in a patient with an active peptic ulcer. But if we put in a phrase such as you suggest, I think this then lends itself to misinterpretation.

Senator NELSON. What?

Dr. HODGES. That the physician may feel that it is more safe to use it in active peptic ulcers than we believe it is.

Senator NELSON. You mean if you said further that there may be rare cases where it might be used, that the doctor should investigate further as to his particular patient, that that would be a weaker warning?

Dr. HODGES. Yes, I would think it would be more open to misuse with that type of labeling than the wording that we have.

Senator NELSON. I guess I won't quarrel about semantics.

Doctor, you gave me an example of a condition when you shouldn't use a certain drug in tuberculosis. Do you have an example of when you would use Indocin for rheumatoid arthritis in a patient with an active peptic ulcer?

Dr. FINKEL. I think it would be very rare. But all the other drugs that are used for treatment of rheumatoid arthritis also cause ulceration. If the patient had developed an ulcer on cortisone, and had also been perhaps on phenylbutazone, and the disease was in a very severe state, not controlled by those drugs, and some drug was required, I think possibly the physician might feel that using an antiulcer regime, which includes diet and various drugs—that he might try Indocin. And, as I indicated, some of the ulcers have healed while the patients were on Indocin.

Mr. GORDON. One more question. "Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration." Are these not warnings, and should they not be included as such, rather than contraindications?

Dr. HODGES. I agree, they are warnings. But we put them in the contraindication section, since it was intended to contraindicate these drugs in peptic ulcer, and the enlargement is giving a reason why it was contraindicated.

Mr. GORDON. Now, you have stated also that you have to make assumptions that the doctor knows this and knows that. Why do you have to make assumptions? Why don't you assume that nobody knows anything?

Dr. HODGES. Well, the average physician has 4 years of medical school, a year as an intern, and then perhaps several years as a resident. I think in 7 or 8 years of training he does acquire a certain amount of knowledge. We learn quite a lot in medical school.

Mr. GORDON. Doesn't the quality of doctors' education vary, and what they know vary? It seems to me that you should gear the insert to the people who might know very little.

Dr. HODGES. Well, if we took this to the ultimate and assumed that every doctor knew nothing, it would mean that we would have to write full sections giving a disease, how you diagnose it, how you treat it, what you look for, and instead of having a package insert it would be at least a chapter if not a whole book.

Mr. GORDON. You are running it into the ground now.

Dr. HODGES. Yes, I agree. But you have to draw the line between the very minimal that perhaps was the case of 25 or 30 years ago, where they simply said, this is what you use the drug for, and this is the dosage, and the other extreme, where you give the thing in such detail that an intelligent lay person could read it and perhaps could get a good background. Somewhere between that you have to draw the line. And I think there are always going to be differences of opinion as to the wording. With any package insert that is written that we approved another physician might feel that we have overstressed some points and understressed others. This is the individuality that there is between physicians even with uniform training.

Senator NELSON. This is one aspect of several problems that we have been exploring.

The question was, assuming that the profession may be adequately informed—and you might be further inquiring as to the effectiveness of package inserts, warnings, the effectiveness one way or another of ads in medical journals—we had the case, as you know, of chloramphenicol where the witnesses who testified, very distinguished men in the field of medicine, estimated that at least 90 percent of the chloramphenicol being prescribed in America was in cases for which it was not indicated.

One of them testified that he thought that 99 percent was prescribed for nonindicated cases. Dr. Goddard said he was at his wit's end to know what to do about adequately warning doctors about the misuse of chloramphenicol. What we are really getting at here is, what ideas do you have for effectively getting the story told to the doctors, when the whole thrust of the drug industry—I suppose it is perfectly natural—is to advertise the drug and sell it, and get it used as broadly as possible. And on each occasion when you review a package insert, or advertising, you are never in the position of fighting with the company to puff their product some more. Your quarrel always is that the firms are using the wrong words, that they are cleverly, by semantics, overselling the product.

And so to say that you assume that the doctor will be informed by the package insert or the ad, the fact of the matter is that for some reason or other he is not. And part of it may not be because the doctor isn't qualified, but rather because he puts great, unjustified confidence in the advertising that he reads, assuming that the great, distinguished companies wouldn't puff their product respecting how and when and under what circumstances it should be used under the assumption that the FDA must be monitoring the advertising, and so forth.

Therefore, he reads the langauge the firm uses and he goes ahead and uses the drug. There can't really be any other reason for chloramphenicol being so widely misprescribed and misused, can there?

If there is, there is something wrong with the medical profession, and something wrong with the FDA, and something wrong with the advertising, or something wrong some place.

I haven't heard from any authority, including the manufacturer of the product, who questions the judgment and educated guesses of the experts that 90 percent of the chloramphenicol used is being administered in nonindicated cases.

Now, what is wrong?

Dr. HODGES. I wouldn't like to give the impression that we feel that every doctor is being adequately informed about every drug. This is a major concern of the Food and Drug Administration.

One step that is being proposed, proposed by the President and most strongly supported by the Commissioner, is the issuance of a compendium, which would make——

Senator NELSON. Let me say, the President endorses my proposal.

Dr. HODGES. Very good.

Senator NELSON. All right.

Since there is so much reliance, obviously, on advertising, much of which is puff advertising, and since there is an indication that the doctors don't read the package inserts, do you think that a compendium which gives a good scientific evaluation in some detail, prepared by an objective, independent source, would be of value to the medical profession?

Dr. HODGES. Yes, I do, sir. At present, as you know, the Physicians' Desk Reference is widely used. It does not substitute for a compendium. It falls far short of the standards that we would assert for a compendium.

If we can realize the objective of a book that provides the same information, that is up to date and that is objective, I think it would be used by physicians.

> Reproduction studies in mice, rats and rabbits showed no effect on fetal development or on the reproduction cycle, although, in rats, there was some decrease in fetal viability. However, since studies in mice demonstrated that this drug crosses the placental barrier and since severe adverse reactions have been noted in some adults, this drug should not be given to pregnant patients.
>
> Indocin should not be administered to children.

As I indicated, the contraindications section is the stronger part. This is where we put the things that are the most important.

Senator NELSON. You indicate that Indocin should not be administered to children. And the FDA recommended for the package insert the wording "Indocin should not be administered to children." However, the firm's labeling ran as follows: "Since the experience with Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established."

I read what the recommendation of the FDA was, and then what was put on the new package insert, saying that Indocin should not be administered to pediatric groups until the indications for use and dosage have been established.

And I would like to read a comment on this by Mr. Raymond Newberry of the FDA. This is addressed to Mr. Kirk, and is dated October 14, 1966:

> As you will recall, we had this in FDA before us last August. The principal thing involved was that the product had been marketed for a year, during which time adverse reactions had mounted considerably. One of the main causes of concern was several deaths of children due to the drug (despite the fact that it had really not been used in very many children).
>
> The Bureau of Medicine was concerned because physicians were abusing the drug by giving it to children despite the contraindications, which read: "Since the experience with Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established.
>
> To me it is small wonder that this drug was (and probably is) being abused by using it in children. The so-called contraindication is, as I mentioned in my August 26th memo, an open indication for doctors to experiment to find the proper use and dosage in pediatric age groups.
>
> The emphasis is, of course, all wrong.
>
> Note that the letter to be signed calls for a new statement which includes the proper reason why this drug should not be used in children. The reason is "because of the possibility of severe and fatal reactions." Nevertheless, the labeling still bears in two separate places the old reason "because of limited experience" and "until the indications for use and dosage have been estab-

lished." In other words, the physicians who use this drug in children are probably legally protected because of the contradictory statements.

(The complete memorandum follows:)

INTRA-ADMINISTRATIVE REFERRAL—ISSUANCE DATE, OCTOBER 14, 1966

REFERRALS AND RECOMMENDATONS

Mr. KIRK: As you will recall we had this NDA before us last August. The principal thing involved was that the product had been marketed for a year during which time adverse reactions had mounted considerably. One of the main causes of concern was several deaths of children due to the drug (despite the fact that it had really not been used in very many children). BM was concerned because physicians were abusing the drug by giving it to children despite the contraindication which read: "Since the experience with Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until the indications for use and dosage have been established."

To me, it is small wonder that this drug was (and probably is) being abused by using it in children. The so-called contraindication is, as I mentioned in my August 26 memo, an open invitation for doctors to experiment to find the proper use and dosage in pediatric age groups. The emphasis is, of course, all wrong.

Note that the letter to be signed calls for a new statement which includes the proper reason why this drug should not be used in children. The reason is "because of the possibility of severe and fatal reactions". Nevertheless the labeling still bears in two separate places the old reasons "because of limited experience" and "until the indications for use and dosage have been established". In other words, the physicians who used this drug in children are probably legally protected because of the contradictory statements.

I wish to point out that this case is very similar to the one made by Abbott for the non-recommended use of Vercyte in leukemia of children where the reason given was "lack of clinical experience in this age group". The real reason was because of a lack of effectiveness which is certainly not as significant as the real reasons given here: "the possibility of severe and fatal reactions". As you may recall the vercyte case was one of these examples used by Dr. Goddard down in Miami to castigate drug firms for false and misleading drug labelling.

Note also that Merck disagreed with our views on several different points, some of which we have apparently reconsidered and have now changed our minds on. The No. 1 item (See Merck letter of 9/2/66) was the warning statement to the pharmacist. The firm argues that there is no reason to single out this drug for such a warning. However, there are other drugs with a similar and sometimes more severe warning statement. One I can think of off-hand is Myleran (busulfan) where the pharmacist is told to place a warning sticker on the drug label when he dispenses it.

There are other things in this labeling that do not appear satisfactory, such as using Indocin as a substitute for salicylates, however, since I have previously pointed out most of these in my 8/26/66 memo, I will not repeat them here.

RAYMOND E. NEWBERRY.

Senator NELSON. Now, my question is, first do you agree with the statement made here by Mr. Newberry? And, second, why did the FDA permit the company to water down the warning which FDA recommended should read, "Indocin should not be administered to children"?

Dr. HODGES. I will answer the questions in reverse order.

We put this warning in because we had some data on children. They had been under study in the investigational stage. There were 40 children studied, and we had seen no severe adverse reactions in any of these children.

The potential of this drug for producing adverse reaction in children certainly was not clear at the time we approved this drug. And such data as we had appeared to indicate that this warning was quite adequate.

Now, when Mr. Newberry submitted his statement—this is an after-the-fact statement—we then had a considerable amount of postmarketing experience, when the drug had been used in children, in spite of our warning against its use in children, and the severe adverse reactions had occurred. At the time he made his statement I think I would agree substantially with what he says. But he could not make that statement when the application was originally approved.

I might say that the application went before the same office in which Mr. Newberry or somebody substituting for him, his predecessor, was in the same place, and when we approved it, they did not make those comments at that time. They had no reason to.

Senator NELSON. If I am correct, however, you did recommend in the beginning that Indocin should not be administered to children, didn't you?

Dr. HODGES. Perhaps Dr. Finkel would like to answer that.

Mr. GORDON. Dr. Finkel, I have here a summary from the FDA files written by you in which you clearly recommend that Indocin should not be administered to children. You must have had a reason for writing that strong contraindication.

Dr. FINKEL. No, the only reason was that there had only been 40 children that had been treated. The exact dosage for pediatric age groups had not been established. There were no unusual side effects.

There were certainly no deaths in those 40 children. This was 40 children out of over 5,000 patients, and we felt that was entirely inadequate to recommend pediatric usage.

Now, with regard to the letter that was issued to the company which stated that Indocin should not be used in children, that statement was not watered down by the company. There was a decision by the Bureau following issuance of that letter that there should be a reason given, not just a flat statement that Indocin should not be used in children.

And so that was the wording that was worked out in the FDA.

Senator NELSON. The FDA changed its mind, then?

Dr. HODGES. No, I don't think so, Senator. In the sentence that appears in the labeling it states that the drug should not be administered to pediatric groups. That is the same thing as saying, Indocin should not be administered to children. But we have added the reasons.

As I have indicated, the deaths were not known at that time.

Senator NELSON. I thought you had recommended that the label should say, "Indocin should not be administered to children." Did you then modify it?

Dr. HODGES. We modified it. But that same statement is still there. Instead of "children" we used "pediatric age groups", which is the same thing.

Mr. GORDON. That first statement isn't there at all. It says, "it is recommended that this drug should not be administered to pediatric age groups." You don't say, in the modified version that it should not be given. There is quite a difference between the two. The statement actually used is considerably weaker.

Dr. HODGES. I think that on the data that we had then, this recommendation is justified and correct. I would not make the same statement today, because we have more knowledge.

Certainly it should not be used in children now. But we were not in a position to say that when we approved this drug.

Senator NELSON. In the data that was submitted in the IND, did I understand you to say that only 40 cases of children were involved?

Dr. HODGES. That is right, Senator.

Senator NELSON. Why, then, wouldn't you just prohibit its use on children until more evidence had been accumulated and submitted by the company?

Dr. HODGES. Well, children, of course, include any one below the age of 14. Some pediatricians say below the age of 16. Among children there is a form of juvenile rheumatoid arthritis which can be quite severe and crippling.

These children then, these severe ones, are often on corticosteroids, and they may develop the severe side effects we see from corticosteroids. Some doctors may feel, particularly with the older children, that they would, taking into account all the warnings that they have, attempt to reduce the steroid doses, or else to eliminate it completely by changing over to indomethacin.

Senator NELSON. Isn't it true of many drugs that the effect on children is different from that on adults, and, of course, the dosage is different?

Dr. HODGES. That is correct. I think the children have a different metabolism. But the older child, the 6- to 12-year-old child, his drug metabolism is quite similar to the adult, but the dosage is less, because the weight is less.

When you go into younger age groups I think you do get into a problem, and the child's body actually handles the drug differently from that of an adult.

Senator NELSON. With that warning what would you expect of the doctor? Would you expect that the doctor under some circumstances would exercise his own judgment and use the drug despite the fact that you say it should not be administered until the indications for use and dosage are established?

Dr. HODGES. Of course we know that they do. I would say that with this warning, the way we would expect it to be interpreted is that this drug normally should not be used in children.

Its use could be considered where the advantages appear to outweigh the disadvantages—and the main disadvantage which I have indicated when we approved this drug was simply that a dosage schedule for use in children had not been established.

I might say that this type of warning is fairly standard for almost all new drugs, many of which have a potential toxicity equal to that of indomethacin.

Mr. GORDON. Are you saying that indomethacin is a toxic drug?

Dr. HODGES. I said it has a potential for toxicity. We know that it has a potential for toxicity.

Mr. GORDON. If it has a potential toxicity, would you say that it is a dangerous drug?

Dr. HODGES. No; I think you are reading a little more into it than I am meaning to say. Toxicity, I think, is a technical term that we use. It reflects my basic background, where in animals we always refer to toxicity, we don't refer to adverse effects, although that is what they are.

In the human the more correct term is adverse effects. But most modern drugs are potent in their toxicity, that is, in their adverse effects as well as in their efficacy. That is what makes approval of them such a critical matter.

Mr. GORDON. Doctor, I am still not satisfied. Now, it is my understanding that a contraindication should be clear and precisely understandable. The statement in the labeling read:

> Since the experience for Indocin in children is limited, it is recommended that this drug should not be administered to pediatric age groups until indications for use and dosage have been established.

Is it your opinion that this meets these standards of clarity and conciseness so that there is no possibility that the doctor would misinterpret this warning or contraindication?

Dr. HODGES. Of course, there is a possibility. In fact from the actual amount of use of the drug in pediatric age groups, this message didn't get through.

Mr. GORDON. So it wasn't a good message; is that right?

Dr. HODGES. It turned out not to be. But we did not know that this drug had the toxicity that it has turned out to have in children. If we had another drug, not indomethacin, but some new drug which was highly effective in rheumatoid arthritis that we approved today, and there had been experience with only 40, 50, or 60 children, if we felt this was inadequate, we would put the same warning on it. If some of them had severe reactions it would be stronger, but if not, if the position was the same as it was in 1965 with indomethacin, we would have the same warning.

But we also have it in the dosage section, so it would be in two places. This is what we do now. We put it both under contraindications and later under dosage, where the physician will look to see how much he should be using.

Senator NELSON. You mean you put the same warning in both sections?

Dr. HODGES. Identical wording. So it is in two places, to emphasize it, to get the message through.

Senator NELSON. So that I understand what you mean by warning, did you intend by this warning that a doctor would under no circumstances give it to children then?

Dr. HODGES. No; I don't think we could interdict its use in children. We didn't have evidence either for or against the use in children at the time that we approved this drug.

Senator NELSON. But the warning says, "should not be administered to pediatric age groups until the indications for its use and dosage have been established." If indications for usage and dosage haven't been established, he shouldn't use it until then, is that what you are saying?

Dr. HODGES. That is right.

Senator NELSON. Aren't you saying that he should not, then, under any circumstances use it?

Dr. HODGES. No, we're not——

Senator NELSON. Are you saying, then, that a physician looking at this should say, well, I don't know what the dosage is, and it hasn't been established and I don't think I should give it to this child, but still allow him to make that independent judgment as an ordinary practicing physician?

Dr. **Hodges.** No; I would think that I would expect unapproved use like this—or I would like to see, let's put it that way, unapproved use like this to be in hands of a rheumatologist. With these patients with juvenile rheumatoid arthritis, fortunately a majority of them are under the care of specialists, because it is a specialized disease. They get into the hands of the appropriate people who are used to dealing with the disease.

These would be people with considerable experience in the treatment of this disease, in the handling of this particular patient. It would not be a more casual use in a patient who just drops into a doctor's office, where he looks and says, "Well, let's try it." That is not the use that we would envisage or sanction at all.

Senator **Nelson.** Do not thousands and thousands and thousands of doctors who are not specialists in the field treat rheumatoid arthritis?

Dr. **Hodges.** Yes, they do.

Senator **Nelson.** Doesn't the advertising go to them?

Dr. **Hodges.** Yes. But the juvenile rheumatoid arthritis, I think, generally will be cared for by a pediatrician, and will be referred very often to pediatricians with special knowledge in this area.

Senator **Nelson.** So do I understand you to say that despite the label, you would anticipate and expect and would not disapprove of people who specialize in the field, experimenting with dosage on children?

Dr. **Hodges.** As I indicated, in specific instances, with some of these children on steroids, they develop a diabetes-like syndrome, they get thinning of their bones, they get pathological fractures of their bones, they develop hypertension and, they retain fluids, they die from the treatment.

In a child like that I think it would be justified to use this drug. But this is a rare instance. And this would be, I hope in the hands of a specialist who, taking everything into account, and having read the background of material available in this label on the drug, would be in a position carefully to use it in this patient and I think rightfully so.

Mr. **Gordon.** I have a question for Mr. Goodrich.

Now, from a legal point of view, let's say for a lawyer who is defending a malpractice suit, would you say that there is a big difference between a contraindication which says something should not be used and something which says it is recommended that it not be used?

Mr. **Goodrich.** I wouldn't want to qualify, Mr. Gordon, as an expert in malpractice. I think that it is clear that one statement is stronger than the other. How it would be handled in a civil liability suit I am not certain.

But I think that in both it would be considered a warning to the physician not to use it as a practical matter in litigation.

Mr. **Gordon.** But the former is considerably stronger than the latter.

Mr. **Goodrich.** Yes, there is no question about that. And we did ultimately strengthen the warning ourselves, as the use in children was recognized, as you yourself know.

Mr. GROSSMAN. I would like to ask you, Doctor—you seem to have a lot more faith in the doctor's ability, pharmacological ability, than some of our earlier witnesses.

We have been listening to some of these words and the vague interpretations. Why can't we come out and say something yes or no? I just can't imagine a doctor in a little town in Nebraska somewhere having to try to analyze, well, what does he mean, is he saying that we should use it or not? Let's say what we mean, do we mean yes or no. I find it hard to believe.

Dr. HODGES. I am afraid that you can never get a clear yes or no in many diseases. It depends upon the severity of the disease. If the patient is dying, and you know he is going to die, as far as one can ever know something like that, anything that will help that patient is justified.

On the other side of the scale, if the patient has just the slightest discomfort from an arthritic condition then, one would not be justified in using it. So I don't think that, with a few exceptions, we can ever get that dogmatic. If we could, medicine would be much simpler, there is no doubt about it.

Mr. GROSSMAN. It just seems that Senator Nelson read "no use unless," should that mean no use at all, and I saw your colleague shake her head, and you said, no use at all.

Dr. HODGES. I can't see my colleague shaking her head. I have got enough to look at in front of me without looking to the side.

There is use in children, under the investigational new drug notice, which we are aware of, and by implication approve since we are not taking any steps to stop it. These are children with this relatively uncommon form of rheumatoid arthritis, but still common enough so that there are many hundreds and perhaps thousands of children with this disease in the United States, and many more throughout the world.

And I am not giving hypothetical examples when I say that a child with this severe problem from the steroids can be brought back to look and act like a normal child. I am quoting case histories that have been sent to us by the firm from investigators.

Mr. GROSSMAN. Mr. Goodrich, do you feel the same way as the doctor? I don't want to divide you. Don't you see these distinctions?

Mr. GOODRICH. I can see the difficulty of the language, of course. But I will have to agree with Dr. Hodges, that on the information he had in 1965, the warning that was given was the one justified by the data. When the evidence of misuse in children and the deaths occurred, we did strengthen the warning.

And Mr. Newberry's memorandum, if you will remember, was written, I believe, in October 1966, or thereabouts. And this is about the time the warning was strengthened.

Mr. GROSSMAN. In this same line, you mention on page 4 of your testimony, you talk about warnings, contraindications—these are all different categories—in the Precautions and Adverse Reaction Section. Again, these distinctions are the real distinctions?

In other words, you have certain criteria within each section?

Dr. HODGES. Yes; we do have criteria. But there are a lot of borderline cases where the thing could go into one or the other. And it depends upon the judgment of the reviewing medical officer.

At the time this labeling was approved we did not have such clear-cut criteria for putting things in each category.

Mr. GROSSMAN. Does my doctor in Nebraska understand the difference between these?

Dr. HODGES. I think that he would understand the difference between a precaution and contraindication. A precaution is—I think just from the English of the word—"you have to be cautious with this, you can still do it." But a contraindication is getting closer to the absolute.

Mr. GROSSMAN. And a warning is further on?

Dr. HODGES. Yes; that is correct.

Mr. GROSSMAN. Thank you.

Senator NELSON. Is my recollection correct on this, that in the IND submitted on this drug there was data from a total of some 5,000 cases involved, including testimonials, uncontrolled studies, and some controlled experience? Is my memory right on that?

Dr. HODGES. Yes; that is correct, 5,000, just over.

Senator NELSON. And of the 5,000 there were 40 children?

Dr. HODGES. That is right, Senator.

Senator NELSON. Why shouldn't it be the precaution on the part of the FDA to simply tell the firm that this drug may not be used in a particular indication until they have submitted whatever is required to show safety and efficacy for the particular case, and that they have to submit the results of a double-blind test conducted by experts in the field under careful supervision? Why shouldn't that be an automatic procedure in a case like that?

Dr. HODGES. I don't think we can say you may not use the drug, we can't order a physician not to use it. We can go quite a long way.

Senator NELSON. Can't you require the company to submit an adequate double-blind clinical study?

Dr. HODGES. If they want to put it in the indications that it can be used in children, then we can—and in this instance we did—require that they demonstrate by further study the safety and efficacy in children. If they don't want to use it in children, I don't think that we could make them do the studies, just in case practitioners were to use it.

Senator NELSON. Is there any reason why you can't say to them, "Since you have submitted cases of only 40 children out of 5,000 case studies in your NDA, we will require on the warning that this should never under any circumstances be used on children—and that is a warning—until such time as you submit adequate studies for us to rely upon?"

Dr. HODGES. Well, I tried to give the reasons why we didn't do this at the time. We felt that we had a very small amount of data, but the little that we had didn't show anything alarming. Subsequent events have shown that there was a false picture, not through any fault that we know of the firm or the investigators.

Senator NELSON. Is 40 cases out of 5,000 in your judgment sufficient to comply with the law which requires proof of both efficacy and safety?

Dr. HODGES. No, we didn't think so. That is why we didn't allow them to put in the labeling that it could be used in children.

Senator NELSON. Then if your conclusion was that it shouldn't be used in children because it wasn't safe, why didn't you say so? Or why didn't you just say, "We don't have enough evidence, and therefore under no circumstances should any physician ever prescribe this for a child until further notice"?

In other words, where is the proof of safety in the submission?

Dr. HODGES. We have tried to indicate as far as we could that the data were not available, the work had not been done to show that this drug was safe and effective in children, therefore it shouldn't be administered to them. If we were to become more absolute and say flatly, a drug should never be used in children under any circumstances until we have the full data from good studies to show that this can be used, this would, I think, go on practically every new drug that is approved, when it is first approved. It would dilute the effect of this warning if we cry wolf with every drug, and subsequently the studies show that it can be used in children, the practitioners will say, FDA says you can't use this in children, and now they say we can.

So what meaning does the warning have? If we are going to be that dogmatic, I think we have to have reasons, we have to have evidence that it will produce adverse effects.

Senator NELSON. I wonder if it is being dogmatic to say that since you had 4,960 cases out of 5,000 on adults, and you were so concerned about the fact that the clinical data included cases of only 40 children, you should have said it should not be used in children.

The fact of the matter is that it was widely used, and it came within the first 200 drugs prescribed in America within, as I recall, a year. And, there were deaths of children from it. You were satisfied with the showing of safety for the 4,960 adults. You weren't satisfied with the proof of safety in children. You gave a warning, which I suppose every doctor ought to take at face value. But we are looking at the failures to do so.

There is something wrong. Even though an intelligent, thoughtful physician should look at your warning and come to the same conclusion that you came to in writing the warning, they don't always do so.

They didn't do it with respect to chloramphenicol, and they didn't do it in this case, and they have failed to do it with others. And all I am saying is that this is your business, and you have to do something about it.

Dr. HODGES. I would certainly agree with what you are saying. And we are concerned about the warnings, the information not getting to the physician. The steps that have been taken over the last few years have been to strengthen the actual statements in this and the other drugs, as I have indicated, to put it in two places so that it increases a chance of it being seen. When we actually have positive evidence we send a letter to the doctor which he certainly should read, so he should be aware of what is happening.

Senator NELSON. In each case the word is "should." Nobody disagrees with that, he should be. But he isn't. So you get the same result on this drug as you did on chloramphenicol, the mild warnings don't do any good.

Dr. Goddard was here, and his answer was that he was at his wit's end as to how to effectively warn physicians about chloramphenicol.

But we shouldn't be at the end of our wits about doing something about this.

In fact, this is the business of FDA full time, with all kinds of people there to do it. Can't you come up with some ideas about a better approach? You obviously do not always effectively compete, in the information you give out, with $800 million spent by the industry on advertising. That is my conclusion.

The testimony at all times is that the medical profession is qualified. And I think highly of the medical profession. And there are a number of people in my family in it. But there is something wrong some place. If the medical profession is adequately trained, then there is something wrong with the information they are getting. Because they are not following your advice, FDA's advice, on this drug or on chloramphenicol. And I am sure we can find a whole lot more before we are through.

And I wish you people over there would give us some advice on what ought to be done about it. The point is that in many cases, at least, the present system just isn't working. What is your suggestion for doing something about it?

I guess we won't go into drug advertising, because we have a witness who will discuss that tomorrow. And that is not your field.

Please go ahead, Doctor.

Dr. HODGES. We inserted the following into warnings:

> Since dizziness and lightheadedness are frequent side effects during indomethacin therapy, patients should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., in the presence of these symptoms.

We felt that the Precautions and Adverse Reactions section required considerable revision and expansion.

(*a*) We recommended that it be stated that headache, dizziness, and lightheadedness are frequent side effects. The submitted insert stated that the severity of these side effects plus other frequent ones (gastrointestinal disturbances) may "rarely" require stopping therapy. We substituted "on occasion."

(*b*) We felt that the submitted labeling strongly implied that the gastrointestinal side effects of the drug are infrequent and minor in nature. Since this is patently not the case, we recommended insertion of the following:

> Indomethacin may cause ulceration, single or multiple in nature, of the stomach, duodenum or small intestine. There have been reports of massive bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, Indocin should be discontinued. In many of the patients with peptic ulceration, there has been a history of peptic ulcer or patients have been on concomitant steroid, salicylates, or phenylbutazone. Possible potentiation by indomethacin of the ulcerogenic effect of these compounds cannot be ruled out at present. However, in some cases there was no history of a previous peptic ulcer, and other drugs were not being given. Reports of bleeding from the sigmoid colon with no known previous pathology, or bleeding from a sigmoiddiverticulum have been received. Many patients develop occult gastrointestinal bleeding, and as a result, a few may manifest mild to moderate anemia. Periodic hematocrit and hemoglobin determinations are recommended in all patients receiving Indocin. Studies in normal volunteers with radioactive chromate-tagged red blood cells showed that this drug did not in experimental studies cause as much blood loss as, for instance, the salicylates.
>
> Perforation of sigmoid lesions (diverticulum, carcinoma) has been reported rarely in patients on indomethacin. A diagnosis of gastritis has been made in

some patients at laparotomy. The occurrence of ulcerative colitis and regional enteritis has been reported in one patient each; and pre-existing ulcerative colitis has worsened in one patient on Indocin. It is not known whether these intestinal lesions can be attributed to indomethacin.

Milder gastrointestinal disturbances (e.g. anorexia, nausea, vomiting, diarrhea or epigastric discomfort) are not uncommon.

(*c*) We recommended that urticaria and angioneurotic edema—those are probably allergic manifestations—be added to side effects.

(*d*) We recommended that a statement be made that the drug may possibly aggravate epilepsy or parkinsonism in patients with these conditions. (This was placed under warnings.)

(*e*) We recommended that the following be added to the discussion of laboratory tests under Precautions and Adverse Reactions:

Transient elevations in alkaline phosphatase, cephalin flocculation and thymol turbidity levels have been noted in some patients and, rarely, elevations of SGOT values. The relationship, if any, to the drug has not been established.

This amounts to changes in liver function tests, the relationship of which to the drugs have not been established.

In addition, we requested further studies in humans to clarify whether any adverse effect on kidney function was produced. We requested controlled clinical trials for osteoarthritis (generalized and of the hip) and synovitis, tendinitis, tenosynovitis, acute bursitis.

Additional data were submitted by the company with regard to controlled clinical trials in osteoarthritis of the hip. The company elected to drop the indications of osteoarthritis of other joints, and of acute bursitis, synovitis, tendinitis, and tenosynovitis from the package insert, although it decided to continue investigational studies in these conditions with the view to eventual submission of data. Numerous conferences were held in the Bureau of Medicine. All of the recommendations for changes in the package insert were adopted. The drug was approved with the revised labeling on June 10, 1965.

Mr. GROSSMAN. May I interrupt you here?

I wonder if you could give us an idea of the percentage of applications you reply to and determine to be incomplete as first submitted? In other words, is this an unusual procedure?

You spent about four pages telling us about the various changes you recommended. Is this unusual?

Dr. HODGES. No, it is not. We receive, I would say, approximately 200 to 250 original New Drug Applications each year, that is, humans have never been involved before. And until just over a year ago we had not for several years approved one the first time it was submitted.

There were major deficiencies in these applications. Many of them were so badly organized that it was difficult to review the data. We made them "not approvable" on a number of different bases, as indicated, bad applications, bad data.

Mr. GROSSMAN. So the submission in this case of Indocin was not any different?

Dr. HODGES. No.

Mr. GROSSMAN. In other words, the amount of paper you spent in discussing the various details is not to show that this is much worse or different than any other case in this particular problem?

Dr. HODGES. No.

Mr. GROSSMAN. Thank you.

Mr. GORDON. Dr. Hodges, in Dr. Finkel's summary[1] of the New Drug Application, she stated that the labeling is grossly inadequate in providing full disclosure of the serious adverse effects of this drug. So apparently before approval of the NDA there was knowledge about the serious adverse effects of the drug, is that correct?

Dr. HODGES. That is right, sir. And what was in the letter that was sent, and the things that I have just read out, these were the inadequacies. And I think some of them have to be corrected.

Mr. GORDON. She also stated that there is a paucity of controlled studies in this NDA. Now, how do you reconcile the admission here of a paucity of controlled studies with the requirements of the law which state that you have to have substantial evidence of safety and efficacy—and the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations?

Dr. HODGES. The next few pages of my testimony are devoted to this very point. And perhaps I should go on with this.

Mr. GORDON. We can come back to this later.

Dr. HODGES. I am sure you will come back to it later.

Since the committee has heard testimony that the data presented did not comply with the legal requirement that the claims of effectiveness be supported by adequate and well-controlled studies, including clinical studies, on the basis of which it could fairly and responsibly be concluded that the drug would have the effectiveness claimed for it, we welcome the opportunity to explain our actions in approving the New Drug Application.

The preclinical and early clinical trials by several investigators established that indomethacin had an anti-inflammatory effect. Indeed, this is so well established today that indomethacin is used as an anti-inflammatory model, along with hydrocortisone, phenylbutazone and salicylates in the study of the potency of new investigational agents and as a basic research tool in studies in inflammation.

A large number of pharmacologic and metabolic studies were performed in animals and man. Toxicity studies were performed in animals—rats, mice, guinea pigs, rabbits, dogs, monkeys, domestic pigs, and chickens, including a 13-month and 30-month study in dogs, 7-month and 18-month study in rats, a 4-month study in monkeys, and a 5-month study in rabbits. In addition, reproduction studies were performed in mice, rats, and rabbits. The toxicity studies revealed that indomethacin, like other anti-inflammatory agents, is capable of causing gastrointestinal ulceration. In the reproduction studies there was no evidence of abnormalities of the offspring.

About 5,000 clinical case reports were submitted. More than 1,000 involved patients with conditions outside the approvable claims, or patients involved in pharmacological or early pilot studies for safety and effectiveness, so they were not tabulated in our evaluation.

A detailed analysis of 3,015 case reports from 97 U.S. investigators and 913 case reports from 34 foreign investigators was made.

Mr. GORDON. Did you check foreign investigators?

Dr. HODGES. We generally don't. We accept their data on its face value. We sometimes know the foreign investigator. If he is a very prominent individual we know him by reputation, or we have met him at meetings.

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[1] Dr. Finkel's summary begins at p. 2949, infra.

This is part of our continuing professional development, going to meetings. We can get an assessment of the individual. But the data, we just have to take the investigator's word for it that they are accurate.

Now, we would not approve an application solely on the basis of data from a foreign investigator, except in the rare instance where a disease is so uncommon in the United States, or just does not occur in the United States, that we could not get U.S. data. But we will accept foreign data in support of U.S. data.

And as you see here, the preponderance is homegrown.

Mr. GORDON. Now, the 5,000 clinical case reports submitted, were these mostly testimonials or were these from controlled studies?

Dr. HODGES. A little later in the summary I try to give some idea of how many were controlled studies, and perhaps we will come to it then, some more accurate figures. The majority of them, though, would not be double-blind controlled studies, the great majority.

Among the 3,015 U.S. patients, serious adverse reactions, leukopenia, gastrointestinal bleeding, perforation of ulcers, were reported in 30. That is approximately 1 percent. Less serious reactions consisted of 1,747 instances. In many cases, however, patients had more than one complaint. The percentage of patients with less serious reactions was about 40 percent. Therapy was discontinued in 7 percent because of side effects. Although the incidence of side effects was high, the majority were transient and did not affect treatment. Similar figures were reported for the foreign premarketing experience.

Many of the reports in the New Drug Application were uncritical, cryptic, or otherwise defective so as to offer little of value to the evaluation—their only usefulness was to provide a basis for a clinical impression about the overt toxicity to the patient. But there were also a number of reports from well-qualified rheumatologists, many of which included objective measurements such as grip strength, walking time, and degree of joint swelling. We concluded that, with the revised labeling, the drug would be safe and effective in the four conditions for which it was approved.

Senator NELSON. May I ask a question, Doctor?

The answer may be obvious. You are talking about 1963. And I am reading from the review by Dr. Hurwitz in 1967. He is reviewing the material upon which the IND was granted in 1963, and saying it was very critical. It may be that you have a different standard now than you had in 1963. But are you familiar with what Dr. Hurwitz said?

Dr. HODGES. Yes. I have a copy of his review.

Senator NELSON. This was written——

Dr. HODGES. Written March 15, 1967.

Senator NELSON. I ask that the whole statement be printed in the record,[1] but he says in part:

> In summary, then, 136 out of 137 studies are grossly deficient in technique, and incapable of standing up to critical examination; it is unfortunate that the company and its predecessors do not use the more sophisticated investigative techniques that have been evolved to evaluate new drugs. These eight volumes with only one good study can in no way be construed to represent an adequate evalua-

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[1] See p. 2902, infra.

tion of indomethacin's efficacy in osteoarthritis and musculo-skeletal syndromes, and further quality research will be necessary to establish efficacy.

In other parts of it he says:

> Examination of this data, however, reveals that most of the submission consists of old controlled studies that were considered inadequate to support efficacy for the original NDA—

And so forth and so on.

Dr. HODGES. He is saying exactly the same thing that we said in 1965. He is referring to the indications that we had disapproved. He is reviewing the same data and reaching the same conclusions. And he is not referring to the indications——

Senator NELSON. Are those the ones that you did approve?

Dr. HODGES. No, sir. And he says osteoarthritis, and that was joints other than the limbs. That is the data which was reviewed. The musculoskeletal syndromes, that is synovitis, is the indication that we turned down, and which was not in the package insert as approved.

Senator NELSON. He comments on further studies on page 2:

> The second study, "Indomethacin in Rheumatoid Arthritis: An Evaluation of the Anti-inflammatory and Side Effects," by Donnelly, et al., in the British Medical Journal, January, 1967, did not verify the previously established efficacy of Indocin in rheumatoid arthritis. This study was a 10-week double-blind crossover comparison of Indocin and placebo with careful controls and a perceptive critical attitude on the part of the authors. No significant anti-inflammatory effect was found.

Dr. HODGES. I don't have that study before me. And of course, we did not have it in 1965. Though it doesn't relate to the original approval, we can give you some brief comments on that study if you would like them.

Senator NELSON. We would be glad to have them for the record. We had testimony last week on the various studies.

Dr. Donald Mainland was here, and Dr. William O'Brien.

Dr. HODGES. Yes; we read that testimony.

Senator NELSON. The conclusion of that study was that in the double-blind test, with aspirin and a placebo, and aspirin and Indocin, the results were about the same, or a little more favorable in some respects using just aspirin.

Do you have a comment on that?

Dr. HODGES. I will when you finish.

Senator NELSON. These tests were made after the NDA was approved. Why shouldn't it be the automatic practice of the FDA to require data from this kind of quality investigation to be submitted with the NDA instead of accepting 5,000 case studies, most of which were testimonials? It is not that testimonials aren't valuable. I understand that.

Dr. HODGES. I think we have to take into account the time that the 5,000 patients were studied.

Many of them were studied before the 1962 amendments, and so would not be subject to our review. We could not offer any comments on them. The efficacy requirements were not then law. So that all that the firm had to do in 1962 was to demonstrate the safety of a drug in order to market it.

In these 5,000 patients I think we will find out that there are three broad classes of subjects who received the drugs. There is first of all a number of controlled studies, which I will give you a summary of in a moment, on the basis of which we felt that we could determine that the drug was effective. That would constitute, I would say, about four hundred, roughly four hundred of the patients would be in that category. The remainder of the 4,000 would be studies in which the drug was used under the careful supervision of a physician. He could get an impression of the efficacy or lack of efficacy of a drug.

You can't give a drug to patients for a year that is ineffective and the patients, in a large series, not see it.

So this the second class, quite a large number, in which the studies were not double-blind controlled or even single-blind controlled, but there was a measure of control.

And then there is a third class of which we don't see so many now, but we still have it occasionally. Once a drug establishes or appears to establish some efficacy, and publications appear in the literature, the doctors and many patients who are not investigated and not really investigational subjects, will write to the manufacturer or to the sponsor and say, I have a patient who is dying, or who is very ill, and this drug is the only thing that will help, let us have some. Ethically it is difficult to refuse these patients. This would constitute perhaps a good number of the thousands that we rejected as being poor from the point of view of studies. They weren't studies. I don't think the sponsor or the manufacturing firm regarded them as such.

We have the same problem today with many drugs. For instance, the pituitary growth hormone, which is in short supply, we have many people write us and say, how can they get it, they want it for their child who is a dwarf. And even though it is not indicated from the background of the particular child they still want to try it. And it is difficult to refuse these people.

The same thing happened with no control from the FDA before 1962.

Now, these are the three groups of patients. I go into this in a little more detail later.

But I would mention other studies where aspirin is used concomitantly, aspirin plus placebo, and aspirin plus Indocin. Aspirin itself is an active drug, and a patient that responds well to one drug isn't necessarily going to respond to another drug.

The same thing happened in a very good British study with steroids. There was no question about the efficacy of steroids in this condition. But one study showed that aspirin plus steroids was very little if any better than aspirin alone. And this is true. I can give you an example which is an oversimplification. If you treat a patient with a strep throat with penicillin and a placebo, and another patient with penicillin and erythromycin, both of these drugs are effective, but the erythromycin will look no better than the placebo in this type of study.

I don't want to take the example I have just quoted too far with indomethacin. But it is just if you are using an active drug you have to be quite cautious in interpreting the results that are obtained.

(The material previously referred to follows:)

MERCK SHARP & DOHME, WEST POINT, PA.—SUMMARY OF SUPPLEMENT

Name of drug:
  Trade—Indocin.
  Generic—Indomethacin.
  Chemical—1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.

Dosage forms and route of administration: 25 mg. capsules for oral use.
Category or use of drug: Anti-inflammatory agent.
Reason for supplement: Revision of labeling to add new indications.
Date of supplement: May 1966.
Material reviewed: NDA Volumes 71 to 78.
Chemist's Summary: See original summary of 6/10/65.
Pharmacologist's Summary: See original summary of 6/10/65.

CLINICAL EVALUATION

The safety of Indocin is not in question at this time, the labeling having recently been extensively revised by the Division of Supplement Review. The present supplement was submitted with the intention of broadening the indications for use of this drug to include acute inflammatory musculoskeletal disorders, and osteoarthritis in general. At present the drug is specified only for osteoarthritis of the hip joint. Seven volumes of data have been included with this submission to substantiate efficacy for the above new indications.

Examination of this data, however, reveals that most of the submission consists of old uncontrolled studies that were considered inadequate to support efficacy for the original NDA. Six new controlled studies are included making a total of six controlled studies and 137 uncontrolled studies. It would seem then that a decision by us regarding efficacy would rely heavily if not completely, on the new studies since the uncontrolled studies have already been disallowed. Review of the latter reveals that in fact they are quite inadequate and totally unallowable as evidence of efficacy of Indocin for the new indications. Further critical consideration of these studies is contained in the bibliography and let it suffice to say here that in general these studies were poorly conceived, poorly evaluated, and the efforts of the various investigators were poorly coordinated.

When one turns to the controlled studies, it becomes disturbingly apparent that they are little better than the uncontrolled group. Three of the studies lack sufficient data to enable the reader to determine whether they were, in fact, controlled. Mention of the word placebo in an article does not confer upon it controlled status; good data showing placebo results is necessary to ensure to the reader's satisfaction that controls were indeed used. The studies by Langkilde and Rossel, Thompson and Bercy, and Buchmann lack adequate data to substantiate that they were indeed controlled studies. Of the remaining three, two studies—those of Dr. Mandarino and Diamond are poorly conceived and evaluated and have no placebo control. None of these five studies substantiates the efficacy of Indocin for the proposed new indications (see bibliography). Only one study, that of Jacobs, is of any value. This sequential analysis seems to indicate a significant therapeutic effect for Indocin in the painful shoulder syndrome.

In summary then 136 out of 137 studies are grossly deficient in technique and incapable of standing up to critical examination; it is unfortunate that the company and its investigators do not use the more sophisticated investigative techniques that have been evolved to evaluate new drugs. These eight volumes with only one good study can in no way be construed to represent an adequate evaluation of the Indocin's efficacy in osteoarthritis and musculoskeletal syndromes, and further quality research will be necessary to establish efficacy.

An additional problem has been posed by the appearance of two articles unfavorable to Indocin during the time that the present supplement was pending. The first article entitled "A three-month trial of Indomethacin in rheumatoid arthritis, with special reference to analysis and inference" was published by the Cooperating Clinics Committee of The American Rheumatism Association in Clinical Pharmacology and Therapeutics January–February, 1967. One-hundred and forty-one patients with Rheumatoid Arthritis were given either Indocin or placebo for a 3 month period in a well controlled double-blind study. In the eight parameters studied, the authors were unable to find statistically significant differences between the 2 groups with the exception of adverse reactions which were more frequent in the Indocin-treated group. This study could well serve as a model for further research in this area. The authors, who seemed relatively free from bias, carefully designed and planned the experiment, which measured many parameters independently. The statistical analysis was delegated to a well-known and respected expert.

The second study, "Indomethacin in Rheumatoid arthritis: An evaluation of its anti-inflammatory and side effects" by Donnelly et al. in the British Medical Journal, January 1967 (p. 69) did not verify the previously established efficacy of

Indocin in rheumatoid arthritis. This study was a 10 week double-blind crossover comparison of Indocin and placebo with careful controls and a perceptive, critical attitude on the part of the authors. No significant anti-inflammatory effect was found.

In view of the wide-spread acceptance of Indocin and its seeming benefit in Rheumatoid Arthritis. it is an unwarranted conclusion to say at this time that the drug is of no usefulness in this disease. However, since these excellent studies cast considerable doubt on the efficacy of Indocin, further studies of equal or better quality and of longer duration are in order to determine the place of this drug in the physician's armamentarium. This revaluation is particularly necessary given the toxicity of Indocin which renders the drug totally unfit for use if a significant therapeutic benefit cannot be established.

REVIEW OF LABELING

The package insert has recently been reviewed in detail and provides adequate information for safe and proper use of the drug. No further consideration of the label is necessary at this time; however, the proposed labeling changes to add new indications are not supported by adequate clinical studies.

CONCLUSIONS

(1) The proposed new indications to the package insert are not supported by adequate data establishing efficacy and should not be allowed to appear in the labeling.

(2) The efficacy of Indocin in rheumatoid arthritis has been seriously questioned by a reliable clinical study.

(3) The safety of Indocin is not in question at this time.

RECOMMENDATIONS

It is recommended that:

(1) The present supplement be declared incomplete on the basis of inadequate data to establish efficacy.

(2) That Merck, Sharp & Dohme be required to submit new well-controlled studies to establish the efficacy of Indocin in Rheumatoid Arthritis.

David Hurwitz, M.D.,
Metabolic and Endocrine, Div./ODS.

Bibliography—NDA 16-059—Indocin, May 23, 1966

I. CONTROLLED STUDIES

1. Mandarino Indocin/Soma Study. In this double-blind controlled study Indocin 25 mg. and Indocin 50 mg. were compared to Soma (Carisoprodol) 350 mg. Patients had a variety of musculoskeletal syndromes such as lumbosacral and cervical back sprain and radiculitis. The author claims a statistically significant increase in relief of these symptoms in the Indocin-treated group as compared with the Carisoprodol treated group. There was no statistically significant difference in side effects among the three groups.

Critical analysis of this study, however, reveals many gross deficiencies in technique and evaluation. In setting up the protocol, the authors did not use any placebo because, it was felt that the patients should not be deprived of some sort of medication. Without use of a placebo, it becomes difficult to establish the actual therapeutic benefit from Indocin. This study was poorly-controlled as the drugs were administered in variable dosage and for variable lengths of time. The fact that no data were recorded for several of the patients in the study and that one patient was switched midstream from one medicine to another indicates a serious lack of rigorous approach to this evaluation. No mention is made anywhere of whether concomitant medication was controlled. It is well known, that patients with this type of pain will attempt self-treatment with drugs such as aspirin, and unless allowance is made for this phenomenon, it can seriously influence the results of the study.

At the other end of this study, the author and statistican display an astonishing naivete in their treatment of efficacy criteria and in their statistical manipulation. The severity of the various parameters measured is graded mild, moderate and severe without any explanation of the criteria used to arrive at this classification. The three parameters of musculoskeletal pain, spasm, and local tenderness are lumped together without any indication of how they were combined to arrive at an overall impression of severity. For example, if a patient had mild spasm, moderate local tenderness and severe musculoskeletal pain, in which category would he be put? The response to treatment is segregated into five categories and no explanation is given of the criteria by which these categories were chosen. Finally, the most heinous error committed is the assignation of numbers to these categories and then the treatment of them as real numbers with addition and division of them to arrive at mean figures which were then assumed to be precise indicators of overall severity and response. This type of statistical manipulation is unallowable in these circumstances and even though a statistically significant difference in the numbers exists, there is no reason to assume that these actually represent significant therapeutic benefit. Additionally the mean number for severity and the mean score for response are not in the same units, and it is impossible to add or subtract them from each other as was done in this study. It is also surprising that no difference in side effects occurred between the two drugs and the different dosages of Indocin. This may reflect poor reporting. The final impression is that this poorly-conceived and carried-out study is totally worthless and does not in the least prove any efficacy for Indocin in the conditions studied.

2. Dr. S. Diamond/Double-blind controlled study, Indocin 50 versus Indocin 25 versus Butazolidin 100 mg.

In common with the previous study this investigation suffers from a poorly set-up protocol, poor patient follow-up and inadequate efficacy evaluation. Statistical techniques used were similar to that of the previous article and do not seem justifiable. In this study of 109 patients, most with a diagnosis of ostcoarthritis, no statistically significant difference between Indocin and Butazolidin was found. Since the efficacy of Butabolidin in these conditions has not been accurately or semi-quantitatively established by rigorous studies, it is not possible to conclude that Indocin is in fact beneficial, even if the study as a whole were well-controlled and had produced valid results. Because of the above deficiencies, one is really unable to draw any conclusion at all from this study.

3. Langkilde and Rossell, "Indomethacin Therapy in Rheumatology". This is a study of 79 patients with various rheumatic disorders. The patients were studied supposedly by a single-blind technique with a placebo control. The authors claimed good results in rheumatoid arthritis, rheumatoid sponrylitis, osteoarthritis and polymyalgia rheumatica. Adverse reactions were found in 24% of the patients and slightly less than one half of these had to discontinue the drug.

This clinical study resembles the previous ones in its poor design and unwarranted conclusions. The authors apparently have no idea of what rigorous clinical study entails in the way of design, follow-up and evaluation. The choice of a single-blind study can be critized on the basis that bias can be too easily interjected into the clinical situation when criteria for effectiveness are so subjective. It is stated that a placebo was given to the patient, but not enough information is available to enable one to ascertain the precise mode of administration or length of time during which the placebo was given. Criteria for response measurement are not given nor does the final data include any information at all about the placebo. It is interesting to note that criteria for objective response assessment were set up in the protocol and apparently not adhered to in the compilation of the final data; for example, the separate statistical analysis submitted by Merck Sharp & Dohme shows that no data on ring size or effect on fever were included although these were supposedly measured. This separate statistical analysis, by the way, is poorly set-up and uses inappropriate statistical techniques. One wonders if the data at all lends itself to this type of statistical analysis. In any case, we have here poorly-controlled study from which it is impossible to draw any meaningful conclusions of efficacy.

4. "Jacobs, J. H. A double-blind trial of the treatment of the painful stiff shoulder with Indomethacin." This paper was read at the Tvrin Symposium June 7th to 9th, 1965. This is a study of 52 patients with a painful shoulder syndrome studied in a double-blind fashion. Results were anlylzed by means of a sequential analysis system in which 26 pairs were compared in four paraemeters: pain, restriction of movement, internal rotation, and abduction. The trial period was one week. Indocin was shown to be significantly better than

placebo in the treatment of this syndrome. In general, this study seemed to be well-designed and does support the efficacy of Indocin for this condition. Adverse reactions were minimal although significantly greater for Indocin than placebo but in no case did they require discontinuance of therapy nor were there any serious or fatal reactions. It is of interest that this is the only acceptable study contained in this submission.

5. Buchman, E. "The Anti-rheumatic effect of Indomethacin." ActaRheumaticlogica Scandinavica 11: 40–52, 1965. This uncontrolled study is improperly included in the group of controlled studies. Eighty-five patients with rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, and gout were studied by the author on a chronic basis. The author claims considerable increase in functional capacity in the rheumatoid arthritis group and dramatic improvement in patients with gout. Patients with rheumatoid spondylitis responded well also. Some patients in each group were also tried on placebo but not in a rigorous or very well-controlled manner; no data was accumulated for the patients while on placebo. Patients with osteoarthritis noticed increased functional capacity on Indocin therapy. Dr. Buchman's bias may be seen in table 6 in which he notes some "non toxic interesting side effects of treatment" in which one patient with 17 years of psoriatic rash cleared completely and one case of pyorrhea in which the loose teeth became fixed after four weeks. One can hardly see how his enthusiasm for the drug could not help but alter results to appear more favorable. Although the author has taken some pains to develop response criteria, his lack of adequate control allows for the interjection of his obvious bias therefore making results difficult to interpret. This study has technical value only and in no way established therapeutic effect for Indocin in the above diseases.

6. Thompson, M. "Further experience with Indomethacin in the treatment of rheumatic disorders," Brit. Med. Journ., Jan. 8, 1966, pp. 81–83. In this study of patients with various disorders 50 patients with osteoarthritis were treated with Indocin for variable periods of time with variable dosage. This study is uncontrolled in spite of the fact that it is included in the control group; there is no evidence any place in the study that a placebo was used in any of the patients. Although 69% of the patients were regarded as having a completely or reasonably successful response to treatment, there is no evidence to support this conclusion except the author's testimony.

II. VOLUME VIII, COMPILATION OF UNCONTROLLED STUDIES

These volumes contain for the most part, report forms and a summary of experience with Indocin in a variety of rheumatic conditions. Favorable results were reported in all diseases considered, among them osteoarthritis bursitis, tendinitis, low back pain, etc. This whole study would seem to be rather haphazard because no attempt was made to set up a well controlled experimental situation. Instead, report forms were apparently distributed to a number of physicians and they were asked to fill them in on certain selected patients. Therefore we find that dosage and time of administration is uncontrolled and that response criteria are vague to the point of being meaningless. That different observers might have a different conception of what constitutes good, excellent and fair response to therapy does not seem to have been considered at all. With the development in recent years of more sophisticated techniques in clinical research it is astounding that Merck Sharp & Dohme would even bother with data from such a poorly designed study. We feel that we have a right to expect more sophistication in evaluating a drug then is expressed here, especially since a recent study rigorously conducted (referred to above) has demonstrated a lack of efficacy of Indocin in Rheumatoid Arthritis. The studies in these volums therefore do not in any way establish efficacy of Indocin in the conditions studied. Volume 8 contains some additional published and unpublished uncontrolled studies that are unacceptable as proof of efficacy.

DAVID HURWITZ, M.D.,
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Dr. HODGES. I shall go on with my testimony, sir.

A decision on safety and effectiveness of a new drug is complex. It involves weighing all of the available data, the nature and natural history of the disease to be treated, the results of the controlled studies ("double-blind," "single-blind," and placebo, and comparison drug), the control of the disease in the patient by previous therapy, and the status of the patient on long-term therapy while under observation by a trained investigator.

As we have said, the majority of the data submitted in the New Drug Application for indomethacin involved studies which were not performed with the "double-blind" or other controlled techniques. These data were acceptable only for the information they imparted relative to safety. They enabled us to view the potential hazards of the drug in a large number of patients—and the larger the patient population the more likely it is that adverse effects will be disclosed. Our total experience with this drug bears this out. In addition, these studies contributed to information on safety over long-term use, since over 700 patients received the drug for more than 6 months and over 200 received it for more than a year.

We were convinced that the drug would be effective, as well as safe, by the more sophisticated studies presented and by the qualifications of the investigators to evaluate drug performance in these diseases.

The available controlled studies, defined here as those in which indomethacin was compared with placebo or a known active drug in single or double-blind fashion are quite a few in number. These are being entered as an exhibit.[1]

Mr. GORDON. Doctor, you say that these studies were quite a few in number. That seems to contradict what Dr. Finkel said. She said there was a paucity of controlled studies. You say they are quite a few in number. How do you reconcile that?

Dr. HODGES. I think there is a paucity in relation to the whole number. Of the 160 or 170 that were carried out by different investigators who used the drug, I have found that there were only—Dr. Finkel found the same thing in 1964—that there were only eight of these studies that were of good quality, they were controlled studies, seven of them were double-blinded, and one of them was single-blind. So eight out of 170, I think, for that I think paucity is a fair term. It is still enough to——

Mr. GORDON. You say they were quite a few in number?

Dr. HODGES. Yes. I think you can argue with what constitutes quite a few. But eight is the actual number.

Mr. GORDON. Let me ask you another question about the qualifications of the investigators. You assume that a good doctor is necessarily a good scientist skilled in conducting tests? Do they both go together?

Dr. HODGES. Not necessarily.

Mr. GORDON. You say that rheumatologists may be good doctors. But does that necessarily make them good drug investigators?

Dr. HODGES. No. Just because someone is skilled in treating patients with rheumatic disease and is an excellent physician doesn't make him an excellent investigator, because in addition to his clinical acumen he has to be able to record his data, to interpret it. And these are not simple things. Just making and keeping a good record alone is a thing that some doctors are not too good at.

Mr. GORDON. But being a good doctor doesn't necessarily make him a good investigator.

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[1] See complete prepared statement beginning at p. 2919, infra.

Dr. HODGES. That is right. But we look to their background a little bit more than that. These people are all people who had published work, they were in general members of the appropriate society, the specialty society that deals with these diseases. They had a very good background in management and in research problems with rheumatic diseases.

Some of these studies were performed and published following approval of the drug. Some of those which were published after drug approval were available to us in preprint form prior to drug approval. Some of the foreign studies published prior to approval were not available to us at that time. Many of these studies were of poor clinical designs. The better studies and the good studies can best be described by brief abstracts made by me of the published papers. More detailed abstracts have been prepared and will be entered as an exhibit. The detailed abstracts include papers published before and after approval. The following papers were available to us in their entirety prior to approval:

I would like to stress that we had all the data available. We did not make any decisions simply based on an abstract or something that was published in a journal, or any other place.

I have summarized the studies that are listed on the following three pages:

Ward, Jr.: Rheumatoid Arthritis: Evaluation of Disease Activity and Response to Indomethacin Therapy.

In a double-blind trial indomethacin was compared with placebo over a 2-month period in 40 patients with rheumatoid arthritis. All received concomitant aspirin, which they had been taking before, but the dose was fixed throughout the study. Indomethacin was significantly better than placebo with regard to pain, morning stiffness, joint tenderness and swelling. There was no effect on grip strength or ring size.

Wanka, J. et al.: Indomethacin in Rheumatic Disease. A Controlled Clinical Trial.

In a double-blind crossover trial using indomethacin and placebo in 22 patients with rheumatoid arthritis, 17 showed preference for indomethacin. The patients were crossed over weekly for a period of 6 weeks. In some patients, grip strength, joint swelling and tenderness improved consistently with indomethacin and deteriorated without it.

Catoggio, P.M. et al.: Indomethacin in Rheumatoid Arthritis: Properties, Side-Effects (Abstract), Arthritis and Rheumatism.

In a double-blind noncrossover study in 33 patients (31 rheumatoid arthritis, two rheumatoid spondylitis) using indomethacin and placebo, the drug was shown to be significantly effective on subjective and objective parameters.

Hart, F. D. and Boardman, P. L.: Indomethacin and Phenylbutazone: A Comparison.

A double-blind crossover study using indomethacin and phenylbutazone (4 weeks on each drug) in 26 patients with rheumatoid arthritis revealed no significant differences between the drugs with regard to relief of symptoms but a greater reduction of morning stiffness on phenylbutazone and a greater reduction of joint swelling on indomethacin.

Percy, J. S. et al.: Indomethacin in the Treatment of Rheumatic Diseases.

A double-blind crossover study in 24 patients using indomethacin and phenylbutazone in patients with rheumatoid arthritis revealed similar response for both drugs subjectively and objectively but more patients expressed a preference for phenylbutazone because of lower incidence of side effects.

Smyth, Charley J.: Indomethacin in Rheumatoid Arthritis. A Comparative Objective Evaluation with Adrenocorticosteroids, Arthritis and Rheumatism.

In a single-blind crossover study indomethacin was compared with placebo. Comparison was also made with corticosteroids. There were 55 patients with rheumatoid arthritis. Results were measured objectively only (ring size, grip strength, walking time and so forth). There was a significant difference between both drugs and the placebo in various parameters (not in all). A comparison of steroid alone against steroid plus indomethacin revealed improvement in certain parameters in the latter group. Indomethacin could be completely substituted for steroids in 16 to 30 patients, and in another four steroid dosage could be reduced.

Abrupt substitution of placebo for indomethacin revealed prompt relapse in 3 to 5 days with suppression when indomethacin was restarted. This maneuver and its results were quite obvious in studies done by Rothermich.

Mr. Gordon. On that same page you summarized the work of Wanka and Dixon by saying, "Indomethacin significantly relieved pain and increased joint motion." I would like to call your attention to a letter to Merck Sharp & Dohme from the Food and Drug Administration dated January 13, 1965, in which you conclude that no conclusions can be drawn from this study. And in addition, there is a memorandum from Dr. Finkel in which this conclusion, based on the author's figures, are at considerable variance with your own conclusions, and so on and so forth. In other words, these examples don't seem to indicate that this particular study was such a good study, or that these figures show what they are meant to show.

Dr. Hodges. I would not like to imply that any one of these studies was a perfect study. I think there are defects in all of the studies that I have listed. And this is true of every study that has been carried out on this drug, including the ones that have been referred to recently, such as those by the Cooperative Clinic. There have been criticisms of all of these studies. The perfect study, double-blind crossover study with this drug has not been done yet. I don't know that it can ever be done absolutely ideally.

On this special study perhaps Dr. Finkel has some comments she would like to make.

Dr. Finkel. The January 5 letter related to the fact that we did not have the raw data from the Wanka-Dixon study, we merely had an abstract, we did not even have the paper. And subsequently a more detailed abstract was submitted. But the tables and figures that were given did not have captions, and I attempted to try to interpret the figures from the abstract.

Finally, the raw data were submitted. And they were found to be in agreement with what was subsequently published.

Mr. GORDON. Also in the next study, the Michotte study, Dr. Finkel said in a memorandum of April 5, 1965—and I ask that all this material be placed in the record at the appropriate places—she said, "The result is unimpressive in rheumatoid arthritis."

Dr. HODGES. They didn't study rheumatoid, it is osteoarthritis.

Mr. GORDON. She says that it was unimpressive in rheumatoid arthritis.

Dr. FINKEL. The studies in rheumatoid arthritis were unimpressive. This paper that we summarized on page 14 dealt with osteoarthritis of the hip.

Dr. HODGES. I will return to the Rothermich study——

Mr. GORDON. These studies that you referred to here on the effect of indomethacin on rheumatoid arthritis, the results——

Dr. HODGES. We agree, not all studies show efficacy of the drug. This is an expected thing. I think in fact one of our criteria for becoming suspicious of a study, or a group of applications, is that if they show such uniform efficacy for a drug, it looks as though it was never carried out. There is a normal variation. As you know, if you carry out a hundred studies, in 5 percent of them, on the criteria you generally employ, you can get chance results that will conflict with what should actually be shown.

The study by Dr. Rothermich on page 13 comprises experience with 216 patients with rheumatoid arthritis—and its variants—rheumatoid spondylitis, gout, and miscellaneous conditions. There were 150 cases reports in the NDA; the published paper gives the investigator's additional experiences. Of particular interest is the 22 patients with rheumatoid arthritis who were involved in a double-blind trial with placebo; as stated by the investigator, 20 did better on indomethacin. In addition, single-blind placebo substitutions were made in 86 patients with rehumatoid arthritis. In 70 of these there was a rapid relapse on placebo. This was verified by repeated trails in 55 patients.

The exhibit that we have relates to this study.

Dr. FINKEL. Dr. Rothermich had a very interesting technique in which he would substitute a placebo when he had gotten a good result And this was criticized last week by Dr. O'Brien, who stated that patients, once their symptoms have subsided, regardless of what you do to them, whether you remove the drug or not, are going to get relapses.

But in the paper that Dr. Rothermich wrote he summarized what we noted in the raw data on 85 patients, and in 70 of those he repeatedly made placebo substitutions, and in 24 to 72 hours he would get an acute relapse. And this was reported by a number of investigators who used the same technique. But I just wanted to demonstrate the kind of things in three tables that were given in Dr. Rothermich's paper.

This is a patient with psoriatic arthritis, which is a variant of rheumatoid arthritis where they also have psoriasis. And this is a short-term study of only 1 week. But there are degrees of severity ranging from zero up to 4 plus, 4 being the more severe. And the patient was started on indomethacin with a drop in the symptoms. And then for 2 days—the dosage was dropped the second day, it was lower than the first day. And so the patient relapsed slightly. On days 3 and 4 the patient was put on placebo, and there was a big rebound up to maximum severity of the disease. On days 5 and 6 the patient was back on indomethacin, and the severity went down, halfway here, and down to zero, and the left hand is black. And that was the most severe involvement.

The other joints are the red line. And this patient didn't have such severe disease.

Then on day 7 the dosage of indomethacin was halved, and the patient developed a marked relapse, but not as bad as on placebo.

Mr. GORDON. Dr. Finkel, it is for one patient?

Dr. FINKEL. Yes. This is just an example.

Mr. GORDON. Now, in the course of treatment of this particular patient, the dosages were changed; is that right?

Dr. FINKEL. Yes. In this particular patient, she was started on 100 milligrams, which is a little higher than they are usually started on now. But the maximum dosage is 200. And the dosage was dropped a little bit, and then she was given a placebo.

Mr. GORDON. Did the patient know what she was getting?

Dr. FINKEL. No.

Mr. GORDON. Did the physician know?

Dr. FINKEL. The physician knew when he was changing to a placebo.

Mr. GORDON. And did he vary the times when he was changing the dosages?

Dr. FINKEL. The drug was given four times a day. So that on days 3 and 4 the patient got her four capsules the way she did on days 1 and 2, but she didn't realize that a substitution had been made.

Mr. GORDON. Was this a real, double-blind controlled study similar to that of the cooperating clinic committee and Dr. Pinal's study and Dr. Donnelly's group in England, in which neither the patient nor the doctor knew what was being used?

Dr. FINKEL. No, it was single-blind. However, Dr. Rothermich, as we indicated, did double-blind studies also. And I was giving you an example of the kind of relapse that can occur when the drug is withdrawn.

Senator NELSON. How was the relapse measured?

Dr. FINKEL. The relapse was measured by a combination of subjective and objective parameters that Dr. Rothermich used.

Mr. GORDON. And what are the subjective parameters?

Dr. FINKEL. The subjective is the degree of pain that the patient experiences, and how much stiffness of the joints, and the duration of morning stiffness. Those are subjective, because you have to ask the patient.

Mr. GORDON. And objective?

Dr. FINKEL. Objective includes joint swellings, redness—in this particular state he didn't measure ring size, but grip strength and walking time are other objective techniques. And I use the word "objective" in quotation marks, because none of them are really objective.

This is a patient with classical rheumatoid arthritis who was treated over a 2-year period. Each one of these boxes represents a month. And here at the start of therapy she was on both phenylbutazone and prednisone, which is a cortisone derivative. And she was at maximum severity of 4 plus. She was then—the phenylbutazone and prednisone were maintained, and she was put on indomethacin. This particular patient required rather high doses, but she was started at a level of

200 milligrams. And she got some minor relief. And the dose was raised, and she improved. And here placebo was substituted without her knowledge, and she flipped up to 4 plus severity.

She was then put back on drug, and she had little mild relapses during the ensuing 3 months. And she was put back on placebo during month 9. And in the meantime, phenylbutazone was withdrawn, and the dosage of the prednisone had been lowered to half of what it was.

During month 9 when she was on placebo she developed a severe relapse up to 4 plus, so they had to increase her dose of steroid. And then she went back on drug and came down.

Now, over month 11 they halved her dose, actually her dose was down to one-third of what it had been. And she developed a relapse. And then she was maintained fairly nicely throughout the remaining 2 years, except that she became a little worse during the last 3 months. And they had to increase her dosage.

I just have one other chart, because the question of gouty arthritis was brought up here last week.

This is a patient with chronic gout treated over a 40-month period. And essentially it is the same thing. When placebo was substituted each time the patient went into a relapse, and when the patient was put back on drug the symptoms subsided.

Mr. GORDON. What is the claim for this experiment by Dr. Rothermich?

Dr. FINKEL. Well, he was just demonstrating that when he substituted a placebo without the patient's knowledge that relapses occurred within 24 to 72 hours. And as I indicated, this is just one investigator. This was reported by a number of investigators who used the same technique, though it is not a double-blind trial.

Dr. HODGES. No, it is a single-blind, the doctor knew it, but the patient didn't.

Senator NELSON. You can't avoid a bias.

Dr. HODGES. No, you can't. And with a single investigator and a single patient, such a study would not have a great value. But if a number of investigators produced this effect in a number of patients on a number of occasions over months and years, it is significant.

Senator NELSON. It doesn't demonstrate anything vis-a-vis any other drugs, aspirin or whatever it may be?

Dr. HODGES. In 20 of the studies it did, because the patients were on both aspirin and indomethacin, and when the indomethacin was stopped the symptoms recurred.

However, I would like to make it clear that we would not approve a drug solely on the basis of these single-blind studies. There was corroboratory evidence.

Mr. GORDON. How about the argument that rheumatoid arthritis is a cyclical type of disease, and by giving the placebo at a particular time you cause the pain to increase, and by giving the drug at another time you can show improvement?

In other words, it is not really controlled, double blind. You can really manipulate it to show what you want to show, can't you?

Dr. HODGES. I wouldn't say manipulate exactly. But I agree with you that this disease is subject to spontaneous remissions. If you happen to put the patient on the drug just before one is going to occur you can say, look what the drug did, and in actual practice it didn't necessarily do anything. But to produce that pattern again and again, as we have here, exacerbation and remission corresponding with periods off the drug and on the drug, while it could be coincidence in a few cases, in a large number, in a larger series with seven investigators, the likelihood that it is a coincidence decreases.

Senator NELSON. Please go ahead.

Dr. HODGES. I have summarized other studies of less quality as far as demonstrating the efficacy is concerned. And there were some in which we found that the investigators found that the drug did not appear to offer any advantage over the placebo.

Rheumatoid arthritis is one of the most difficult diseases in which to evaluate a drug. Rheumatologists cannot agree on the best clinical design for anti-inflammatory studies. Even the so-called objective techniques used in evaluating results of therapy, such as measuring grip strength and walking time are subject to extraneous factors of the patient's mood, time of day, and so forth. One cannot always substitute statistical results of a short-term study for long-term followup of patients by expert rheumatologists who know their patients. This is not, of course, to imply that controlled studies should not be done. Our recommendations for anti-inflammatory agents include double-blind placebo-controlled and positive-controlled studies for at least 3 months and—that is at least 3 months on each drug, usually—in some studies, a crossover design following a period without drug therapy (or just basic salicylate therapy) ; we recommend pairing patients, to the degree possible, as to age, duration of the disease, severity of disease, sex, response to previous therapy; we recommend evaluation based upon the patient's subjective findings, objective techniques, and ability to withdraw previous therapy. We also recommend that patients be requested to keep a record of their salicylate intake.

Mr. GORDON. Here you have laid out the requirements for the tests. Now, why didn't you request this from the investigators in the first place?

Dr. HODGES. To a certain extent we apply these criteria to the studies that were done. And as I indicated earlier, many of the studies have shortcomings. I am not trying to say that they were perfect studies. But they were adequate to demonstrate the efficacy of the drug. I don't think any of the recent studies meets the criteria that we have put down here. These are suggestions made by us, and I would say made by us in the light of experience of the last few years. And FDA evaluation of these drugs is improving in its sophistication just as clinical pharmacology is improving in its sophistication.

Mr. GORDON. Are you saying that the techniques used in the three studies were not known in the early 1960's?

Dr. HODGES. No, I am not. But the criteria that we have spelled out, the total criteria, while they were known, they certainly were not widely accepted and widely carried out in the early 1960's.

Mr. GORDON. You would demand them now, wouldn't you?

Dr. HODGES. We look for them now. We can't always demand them. We get as close as we can to them. Supposing we had the three expert witnesses who testified here last week draw up a study that didn't include some of the features we have here. It would be difficult to say that their study was not acceptable. We would certainly accept it. It might demonstrate results at least as well as a study that we have here.

This is just one way of doing it that we think is a very good way, a desirable way. But we would not mind an investigator or a sponsor doing this study and no other. And we wouldn't mind him doing the study with other modifications.

Mr. GORDON. Are you saying that you can't insist that they follow certain procedures?

Dr. HODGES. If we were to feel that there is absolutely no other way to demonstrate efficacy, we could insist.

Mr. GORDON. Do you participate in the designing of the studies which are going to be presented to you?

Dr. HODGES. We certainly didn't before 1963, because we didn't have the control over the investigational drugs. In the years after approval, because of the great mass of investigational new drug notices that were received, we were just not able to do this, we didn't have the time. In the last 2 years we have done this more and more. We have indicated publicly to the drug firms that we wanted to do this, we were willing to do this. And they wanted it, too. They come in, and we sit down, and we may spend an afternoon with a half a dozen or a dozen people from each side going over the studies and the details of the studies to come up with what we feel, the experts on both sides, as nearly as possible, to be the ideal study to demonstrate what we want.

Now, these are all prospective.

Senator NELSON. Is this at the time of the IND?

Dr. HODGES. Nowadays, yes, at the time of the IND, before they go into phase 3. In other words, in phase 1 they demonstrate the safety. In phase 2 they demonstrate that it seems to have some effect on disease. And then they go on to try and find the right dose for the right disease. That is the stage where we will meet with them, are happy to meet with them to try to design us closely as we can the perfect study. But it is all prospective.

When the study is completed we may well look back and say. "Well, I wish that we had added so and so, I wish we had used all these criteria as well." I think we will always have that.

Senator NELSON. But at the time of the conference, at the time of the IND, you have it within your power to effectively specify some particular methodology that you want since, if you aren't satisfied with what they are producing, you can turn down the application?

Dr. HODGES. Yes, we do. Where we indicate criteria or methods, then I think the onus is on the sponsor to show that his method is better. Sometimes they do.

Senator NELSON. For the purposes of the record, at some stage I would like to put in Dr. Hurwitz' comment on these studies that were made of this drug.[1] This is a year ago, January 25, 1967. And he comments on the studies by Donnelly, and the Nieman study, and concludes by saying:

> However, since these excellent studies cast considerable doubt on the efficacy of indomethacin, further studies of equal or better quality and of longer duration are in order to determine the place of this drug in the physician's armamentarium.

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[1] See p. 2902, supra.

This re-evaluation is particularly necessary given the toxicity of indomethacin which renders the drug totally unfit for use if a significant therapeutic benefit cannot be established.

Do you have any comment on that statement by Dr. Hurwitz?

Dr. HODGES. We would be pleased to submit a copy of this for the record, of the full review by the medical officer.

Senator NELSON. We have that. We will put it in the record.

Dr. HODGES. Also, there is a subsequent review by the same medical officer, which I believe corrects or amends some of the statements he made there, to the effect that he believes that subsequent studies demonstrate the efficacy. This was after marketing, and it is not within the purview of my office.

Senator NELSON. These are studies after Mainland and after——

Dr. HODGES. No; it is a review afterward. I don't know if he made another review based on the same studies, or if he had further studies.

Dr. FINKEL. He went back and reviewed the studies that were submitted with the application, and concluded that those studies demonstrated that the drug was effective. It was in August 1967.

Senator NELSON. August 1967.

Do you have that?

Dr. HODGES. We will obtain a copy for you.

(The information referred to follows:)

INDOCIN IN RHEUMATOID ARTHRITIS

Since its introduction in March of 1965, Indocin has enjoyed wide public acceptance as an anti-arthritic agent. Early pharmacologic studies had indicated an unprecedented potency when the drug was used to control inflammation in various animal models. It was hoped, at that time, that Indocin would have a high therapeutic ratio and thus offer a significant advantage over corticosteroids with their multiplicity of serious adverse reactions. Unfortunately, Indocin has shown a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity. This toxicity has been well documented and is now well-appreciated by the medical profession, and Indocin has taken its place along side aspirin and phenylbutazone as another useful agent in a group of poorly understood diseases not amenable to any definitive therapy.

At no time, however, was the actual efficacy of Indocin questioned. It was appreciated that the drug worked considerably better in acute inflammatory conditions like gout than in the chronic arthritics such as rhematoid arthritis, but the drug was believed efficacious in the latter condition. Several new studies published in the first quarter of 1967 in major scientific and medical journals now dispute the usefulness of this drug in rhematoid arthritis. Chief among these is an exhaustive clinical study carried out by the Cooperating Clinics Committee of the American Rhematism Association in association with Dr. Donald Mainland, a well-known biostatistician. This exhaustive study involved 141 patients treated for a three-month period and required ten months to be completed. Indomethacin was compared in a double-blind fashion with a placebo, the patients being allowed free use of aspirin as needed. Although many different parameters were measured and studied by sophisticated statistical techniques, the authors were unable to find any statistically significant differences in these parameters between Indocin and the placebo medication.

In the same month, Donnelly et al. published a similar study in the British Medical Journal. The British authors used a double-blind crossover study comparing Indocin with a placebo, and they also were unable to establish any statistically significant difference between Indocin and placebo. In neither study were there any serious reactions to the medications.

In a third article by Pinals and Frank no differences was found between Indomethacin and aspirin in the treatment of rheumatoid arthritis. This study was a double-blind crossover type and was not as thorough or as well planned as the previous two studies. The authors arrived at the conclusion that Indocin and aspirin have no significantly different effect on the parameters measured which is justified by the results of the experiment, but they seem to have missed the obvious conclusion that no therapautic effect was demonstrated for either of the medications. The measured parameter, while not varying significantly between the Indocin-treated group and the aspirin treated group, also did not vary significantly within each group at two weeks and four weeks. The lack of inclusion of base line data adds a further difficulty to the interpretation of this paper. In contrast to this study, however, the Mainland and the Donnelly studies were well-planned, well-controlled, and seemed to be products of rigorous, thoughtful research.

Indocin's potential toxicity would make its use in rheumatoid arthritis unacceptable if indeed it has no efficacy for this condition. Therefore it was deemed necessary to review the original studies establishing efficacy in this disease. A search of 100 volumes of the NDA revealed six acceptable controlled studies, five of them double-blind the other single-blind. All of these studies claimed efficacy for Indocin but they vary in quality. As a whole, they would seem to indicate efficacy in this condition; results are summarized in the table below.

In comparing the old studies to the new ones, it is obvious the latter are better-controlled and use more sophisticated methods of evaluation. Because of the extremely variable nature of the disease and the consequent difficulty in evaluating modes of therapy, it is impossible to say that the new studies outweigh the old, particularly in view of the large mass of testimonial data indicating efficacy. While testimonal studies are not in themselves adequate to allow approval of a drug by the FDA, they certainly cannot be disregarded as meaningless when the ultimate usefulness of the drug and its success is determined by individual patient reaction to the medication. We are therefore faced with the dilemma of a drug whose efficacy has been seriously questioned by excellent studies but which enjoys solid acceptance by the medical community and the patients it treats. At the present time, then, it would seem wise to consider Indocin as probably effective in rheumatoid arthritis pending further studies in this area. The drug is at the present time safe for use in this condition since in the dosages commonly employed there is very little risk of a serious adverse reaction. This author has recommended in the summary of the most recent supplement submitted by Merck, Sharp & Dohme that further studies be carried out to determine the efficacy of Indocin in rheumatoid arthritis.

DAVID HURWITZ, M.D.,
Metabolic & Endocine Div./ODS.

TABLE I.—INDOCIN REVIEW: CONTROLLED BLIND STUDIES FROM ORIGINAL NDA

Author	Date	Volume	Number of patients	Type	Results	Comment
Hart, F. D., and Boardman, P. L. (Brit. Med. Jour. 11:1281, 1965).	1965	30	18	Double-blind crossover comparison with phenylbutazone, 56 days.	(1) Little difference between drugs in therapeutic or adverse effects. (2) Indocin had greater effect on reduction of joint swelling. (3) No serious reactions.	Data not included with study (has been published with adequate data).
Percy, J. S., Stephenson, P., Thompson, M. (Ann. Rheum. Dis.) (23:226, May 1964).	1964	30	24	Double-blind crossover sequential comparison with phenylbutazone.	(1) No significant difference between drugs in patient preference or grip strength. (2) Phenylbutasone had lower incidence of adverse reactions (none serious in either group).	Data incomplete as regards grip measurement or preference. It would be desirable to see how parameters were measured and actual figures; without these we are unable to tell if the patients improved.
Wanka, J., Jones, L., Wood, P., Dixon, A.	1964	30	22	Double-blind crossover comparison with placebo, 6 weeks.	(1) Patients preferred Indocin but no measurable difference in grip strength. (2) No significant reactions.	The ARA Committee has noticed a feeling of well-being in patients on Indocin. Is this the case here? No objective benefit was noted in the single measured parameter-grip strength.
Ward, J. R.	1965	30	Studies (1) 29; (2) 40.	2 studies double-blind crossover comparison with placebo. In study No. 1, unlimited and irregular use of aspirin and steroids was permitted. Study No. 2 all patients on fixed aspirin and prednisone dosage, 4 months.	(1) Indocin group had less tenderness and morning stiffness. (2) Indocin group had significant decrease in pain, morning stiffness, swelling, tenderness. (3) No significant reactions.	(1) Results variable, uncontrolled use of aspirin and prednisone in study No. 1 make it invalid. (2) Data scant inadequate placebo effect (nil). Validity of statistics, questionable dosage of other medications unspecified (study No. 2).
Smyth, C. J.	1965	47	55	Single-blind variable time several weeks to several months.	Indocin effective in several parameters as compared to placebo.	(1) Well-developed response criteria. (2) Large unwieldy amount of data. (3) Poorly controlled, variable dosage and length of administration. (4) Results only suggestive to efficacy.
Bode, J. J.		80	27 total; 15 on Indocin.	Double-blind, 3 months.	(1) Indocin group had decrease joint tenderness and pain, no difference in parameters. (2) No serious reactions.	(1) Did patients use other medications during this long study?

TABLE II.—INDOCIN: NEW STUDIES QUESTIONING EFFICACY

Author	Date	Volume	Number of patients	Type	Results	Comment
Pinals, R. S., Frank, S. (NEJM, March).	1967		24	Double-blind crossover comparison with aspirin, 2 months.	(1) No difference between Indocin and aspirin. (2) No serious reactions.	(1) No baseline data. (2) Neither drug had any clinical effect which makes results difficult to interpret; authors did not discuss this point. (3) 5 patients on steroids.
Donnelly, P., Lloyd, K., Campbell, H. (Brit. Med. Journal, January 1967).	1967		30	Double-blind crossover comparison with placebo, 1 month.	(1) No statistical significant difference between Indocin and placebo. (2) Some delay in onset of fatigue on Indocin but not statistical significant (3) No serious reactions.	(1) Well-designed study, well controlled. (2) Used aspirin in all patients but amount was recorded and evaluated statistically.
Mainland et al. (Clin. Pharm. and Therapeutics, January 1967).	1967		141	Double-blind comparison with placebo, 3 months.	(1) No statistically significant difference between Indocin and placebo. (2) No serious reactions.	Use of aspirin reduces sensitivity of experiment and may mask small differences between placebo and Indocin.

Dr. HODGES. The cause of rheumatoid arthritis is unknown. In temperate countries the incidence among those 15 years of age or older is about 1 percent for "definite" and 3 percent for "probable" rheumatoid arthritis. Projecting these figures for the United States, there may be approximately 1.4 million people over the age of 15 with definite, and another 4.2 million people with probable, rheumatoid arthritis. Among young adults, females are more commonly affected than males but the incidence in the latter rises with age. Many patients become incapacitated. In one study, 58 percent were unable to engage in their ordinary occupations or household duties.

Rheumatoid arthritis is a systemic inflammatory disease. It is not limited only to the joints but can also involve arteries throughout the body leading to peripheral involvement of the nerves and gangrene of the extremities, and occasionally a fulminant, fatal, generalized arterial involvement. It may involve the heart, leading to inflammation of the membrane covering the heart, congestive heart failure, and other heart disturbances.

Senator NELSON. I have no further questions related to the balance of your testimony, unless there is something in the balance of your testimony you want to elaborate on.

Dr. HODGES. I would like to go over to page 22 and to our conclusions.

We previously discussed other means of therapy, and the toxicity, and the adverse effect of those, to attempt to place in proportion the place of this drug.

Taking into account the drugs that were available in 1965 for the patient with rheumatoid arthritis, bearing in mind the limitations of this therapy and the hazards that were encountered in their use, we concluded that there were sufficient data from adequate, controlled studies to support the conclusion that indomethacin would be safe and effective for some patients with rheumatoid arthritis.

The labeling contained enough information on effectiveness and adverse reactions to enable the physician to utilize his professional judgment in selecting the patients who would be expected to benefit from this medication. These patients would be those who had obtained little or no relief from salicylates or other agents. They would be patients who had experienced adverse reactions to other agents. They would be patients in whom it was considered desirable to attempt to substitute indomethacin for other agents (or decrease the dose of other agents) to reduce the possibility of adverse reactions to the other drugs. They would be patients in whom it was considered desirable to use a drug which did not produce some of the serious side effects of other available drugs. On that basis, the New Drug Application was approved. Our final evaluation was that indomethacin could be approved for use in rheumatoid arthritis, acute and chronic gout, rheumatoid spondylitis, and osteoarthritis of the hip.

The drug is effective only for the control of inflammation and pain in selected patients. Its therapeutic index, that is, the ratio of desirable effects to undesirable effects, places the drug in the middle of the spectrum of drugs used in the treatment of rheumatoid arthritis. The ultimate drug for the treatment of this disease has not yet been identified.

As with all drugs used in the management of rheumatoid arthritis, more extensive clinical experience has revealed new hazards and has further defined the conditions of expected effectiveness for indomethacin.

Dr. Jennings will deal with postmarketing experience.

Thank you very much.

(The complete prepared statement of Dr. Hodges follows:)

STATEMENT OF DR. ROBERT M. HODGES, DIRECTOR, OFFICE OF NEW DRUGS, BUREAU OF MEDICINE, FDA

Mr. Chairman. I appreciate this opportunity of appearing before you this morning to discuss the approval of the New Drug Application for Indocin, Merck, Sharp and Dohme's brand name for indomethacin. For the sake of brevity, with your permission, I will submit for the record a statement of my educational and professional background.

As the name implies, the Office of New Drugs, which is under my direction, reviews all Investigational and New Drug Applications for drugs prior to their introduction to the market.

Clinical trials with indomethacin were underway at the time the new requirements of the Kefauver-Harris Drug Amendments and the investigational new drug regulations became effective in 1963. Many of the early studies and much of the clinical data in the New Drug Application thus reflect a different kind of clinical investigation than that required under the 1963 regulations.

On May 3, 1963, the IND for Indomethacin was submitted by Merck, Sharp and Dohme. It showed that the investigation was in phase 3. clinical trials. The preclinical data were adequate and the clinical trials were being conducted by a number of well qualified rheumatologists. A year later, on June 5, 1964, the New Drug Application was submitted. In accordance with our regulations, the firm was required to submit the names of all investigators who had received the drug, along with the results of all investigations, or an explanation if any were omitted.

The New Drug Application was a voluminous document. It was submitted for use of the drug in rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis (generalized and of the hip), gout, acute bursitis, synovitis, tenosynovitis and tendinitis.

There were extensive studies of the application and in January 1965 it was ruled incomplete (i.e., non-approvable) until further data were submitted and until clarification of possible adverse effects on kidney function had been elucidated. The package insert was considered inadequate in that it did not present a true picture of the contraindications, warnings, precautions, adverse effects, toxicity, and in that it did not exclude the use of the drug in children. In addition, the firm's discussion of the clinical studies in the insert was not balanced; too much weight was given to favorable results.

The following changes in the proposed package insert were recommended in a letter to the company on January 13, 1965:

1. Deletion of all claimed indications other than rheumatoid arthritis, rheumatoid spondylitis and gout. (That is, deletion of osteoarthritis, generalized and of the hip, acute bursitis, synovitis, tenosynovitis and tendinitis). (Later, osteoarthritis of the hip was permitted following submission of controlled studies.)

2. Modification of the claims under Rheumatoid Spondylitis. The proposed package insert stated that Indocin "usually" produces marked relief of pain and improved motion of the spine within 3 to 10 days "in most patients." We modified the "usually" to "frequently" and deleted "in most patients."

3. Modification of the claims under Gout. The submitted insert stated that in acute gout, marked reduction of pain "*is usually*" obtained within 2 to 4 hours. We substituted the words "*may be*". Further, during a discussion of the interval phase of gout, it was stated that indomethacin plus a uricosuric agent "*usually*" provides relief of pain and prevents recurrence of acute attacks. We substituted "*may provide*".

4. We felt that the Contraindications section was too brief and did not include a true picture of the toxic potential of the drug. We recommended that this section be revised and considerably expanded as follows:

"As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration. For these reasons it should not be given to patients with active peptic ulcer. Inasmuch as this drug may cause irritation of the gastrointestinal tract, it is also contraindicated in patients with gastritis, ulcerative colitis and regional enteritis. Indocin is contraindicated in patients with renal disease, psychosis, or marked emotional instability, and central nervous system diseases such as epilepsy and parkinsonism. It is also contraindicated in patients with a history of blood dyscrasia.

"Reproduction studies in mice, rats and rabbits showed no effect on fetal development or on the reproductive cycle, although, in rats, there was some decrease in fetal viability. However, since studies in mice demonstrated that this drug crosses the placental barrier and since severe adverse reactions have been noted in some adults, this drug should not be given to pregnant patients.

"Indocin should not be administered to children."

5. A statement on use in pregnant patients was moved by us from Warnings to Contraindications. We inserted the following into Warnings:

"Since dizziness and lightheadedness are frequent side effects during indomethacin therapy, patients should be cautioned against operating motor vehicles or other machinery, climbing ladders etc. in the presence of these symptoms."

6. We felt that the Precautions and Adverse Reactions section required considerable revision and expansion:

(*a*) We recommended that it be stated that headache, dizziness and lightheadedness are frequent side effects. The submitted insert stated that the severity of these side effects plus other frequent ones (gastrointestinal disturbances) may "*rarely*" require stopping therapy. We substituted "*on occasion.*"

(*b*) We felt that the submitted labeling strongly implied that the gastrointestinal side effects of the drug are infrequent and minor in nature. Since this is patently not the case, we recommended insertion of the following: "Indomethacin may cause ulceration, single or multiple in nature, of the stomach, duodenum or small intestine. There have been reports of massive bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, Indocin should be discontinued. In many of the patients with peptic ulceration, there has been a history of peptic ulcer or patients have been on concomitant steroid, salicylates or phenylbutazone. Possible potentiation by indomethacin of the ulcerogenic effect of these compounds cannot be ruled out at present. However, in some cases there was no history of a previous peptic ulcer, and other drugs were not being given. Reports of bleeding from the sigmoid colon with no known previous pathology, or bleeding from a sigmoid diverticulum have been received. Many patients develop occult gastrointestinal bleeding, and as a result, a few may manifest mild to moderate anemia. Periodic hematocrit and hemoglobin determinations are recommended in all patients receiving Indocin. Studies in normal volunteers with radioactive chromate-tagged red blood cells etc. etc.

"Perforation of sigmoid lesions (diverticulum, carcinoma) has been reported rarely in patients on indomethacin. A diagnosis of gastritis has been made in some patients at laparotomy. The occurrence of ulcerative colitis and regional enteritis has been reported in one patient each; and pre-existing ulcerative colitis has worsened in one patient on Indocin. It is not known whether these intestinal lesions can be attributed to indomethacin.

"Milder gastrointestinal disturbances (e.g., anorexia, nausea, vomiting, diarrhea or epigastric discomfort) are not uncommon."

(*c*) We recommended that urticaria and angioneutronic edema be added to side effects.

(*d*) We recommended that a statement be made that the drug may possibly aggravate epilepsy or parkinsonism in patients with these conditions. (This was placed under Warnings.)

(*e*) We recommended that the following be added to the discussion of laboratory tests under Precautions and Advense Reactions:

"Transient elevations in alkaline phosphatase, cephalin flocculation and thymol turbidity levels have been noted in some patients and, rarely, elevations of SGOT values. The relationship, if any, to the drug has not been established."

In addition, we requested further studies in humans to clarify whether any adverse effect on kidney function was produced. We requested controlled clinical trials for osteoarthritis (generalized and of the hip) and synovitis, tendinitis, tenosynovitis, acute bursitis.

Additional data were submitted by the company with regard to controlled clinical trials in osteoarthritis of the hip. The company elected to drop the indications of osteoarthritis of other joints, and of acute bursitis, synovitis, tendinitis and tenosynovitis from the package insert, although it decided to continue investigational studies in these conditions with the view to eventual submission of data. Numerous conferences were held in the Bureau of Medicine. All of the recommendations for changes in the package insert were adopted. The drug was approved with the revised labeling on June 10, 1965.

Since the Committee has heard testimony that the data presented did not comply with the legal requirement that the claims of effectiveness be supported by adequate and well-controlled studies, including clinical studies, on the basis of which it could fairly and responsibly be concluded that the drug would have the effectiveness claimed for it, we welcome the opportunity to explain our actions in approving the new drug application.

The preclinical and early clinical trials by several investigators established that indomethacin had an anti-inflammatory effect. Indeed, this is so well established today that indomethacin is used as an anti-inflammatory model, along with hydrocortisone, phenylbutazone and salicylates in the study of the potency of new investigational agents and as a basic research tool in studies in inflammation.

A large number of pharmacologic and metabolic studies were performed in animals and man. Toxicity studies were performed in animals—rats, mice, guinea pigs, rabbits, dogs, monkeys, domestic pigs, and chickens, including a 13 month and 30 month study in dogs, 7 month and 18 month study in rats, a 4 month study in monkeys, and a 5 month study in rabbits. In addition, reproduction studies were performed in mice, rats and rabbits. The toxicity studies revealed that indomethacin, like other anti-inflammatory agents, is capable of causing gastrointestinal ulceration. In the reproduction studies, there was no evidence of abnormalities of the offspring.

About 5,000 clinical case reports were submitted. More than 1,000 involved patients with conditions outside the approvable claims, or patients involved in pharmacological or early pilot studies for safety and effectiveness, so they were not tabulated in our evaluation.

A detailed analysis of 3,015 case reports from 97 U.S. investigators and 913 case reports from 34 foreign investigators was made.

Among the 3,015 U.S. patients, serious adverse reactions (leukopenia, gastrointestinal bleeding, perforation of ulcers, etc.) were reported in 30. Less serious reactions consisted of 1,747 instances. In many cases, however, patients had more than one complaint. The percentage of patients with less serious reactions was about 40%. Therapy was discontinued in 7% because of side effects. Although the incidence of side effects was high, the majority were transient and did not affect treatment. Similar figures were reported for the foreign premarketing experience.

Many of the reports in the New Drug Application were uncritical, cryptic, or otherwise defective so as to offer little of value to the evaluation—their only usefulness was to provide a basis for a clinical impression about the overt toxicity to the patient. But there were also a number of reports from well-qualified rheumatologists, many of which included objective measurements such as grip strength, walking time, and degree of joint swelling. We concluded that, with the revised labeling, the drug would be safe and effective in the four conditions for which it was approved.

A decision on safety and effectiveness of a new drug is complex. It involves weighing all of the available data, the nature and natural history of the disease to be treated, the results of the controlled studies ("double-blind", "single-blind," placebo, and comparison drug), the control of the disease in the patient by previous therapy, and the status of the patient on long-term therapy while under observation by a trained investigator.

As we have said, the majority of the data submitted in the New Drug Application for indomethacin involved studies which were not performed with the "double-blind" or other controlled techniques. These data were acceptable only for the information they imparted relative to safety. They enabled us to view the potential hazards of the drug in a large number of patients—and the larger the patient population the more likely it is that adverse effects will be disclosed. Our total experience with this drug bears this out. In addition, these studies contributed to information on safety over long-term use, since over 700 patients received the drug for more than 6 months and over 200 received it for more than a year.

We were convinced that the drug would be effective, as well as safe, by the more sophisticated studies presented and by the qualifications of the investigators to evaluate drug performance in these diseases.

The available controlled studies, defined here as those in which indomethacin was compared with placebo or a known active drug in single or double-blind fashion are quite a few in number. These are being entered as an exhibit. Some of these studies were performed and published following approval of the drug. Some of those which were published after drug approval were available to us in preprint form prior to drug approval. Some of the foreign studies published prior to approval were not available to us at the time. Many of these studies were of poor elinical designs. The better studies and the good studies can best be described by brief abstracts made by me of the published papers (see below). More detailed abstracts have been prepared and will be entered as an exhibit. The detailed abstracts include papers published before and after approval. The following papers were available to us in their entirety prior to approval:

Ward, J. R.: Rheumatoid Arthritis: Evaluation of Disease Activity and Response to Indomethacin Therapy, International Symposium on Non-Steroidal Anti-Inflammatory Drugs, Exc. Med. Found. p. 353–360, 1965.

In a double-blind trial indomethacin was compared with placebo over a 2 month pd. in 40 patients with rheumatoid arthritis. All received concomitant aspirin, which they had been taking before, but the dose was fixed throughout the study. Indomethacin was significantly better than placebo with regard to pain, morning stiffness, joint tenderness and swelling. There was no effect on grip strength or ring size.

Wanka, J. et al: Indomethacin in Rheumatic Diseases. A Controlled Clinical Trial, Ann. Rheum. Dis. 23: 218–225, 1964.

In a double-blind crossover trial using indomethacin and placebo in 22 patients with rheumatoid arthritis, 17 showed preference for indomethacin. The pts. were crossed over weekly for a period of 6 wks. In some pts., grip strength, joint swelling and tenderness improved consistently with indomethacin and deteriorated without it.

Catoggio, P. M. et al: Indomethacin in Rheumatoid Arthritis: Properties, Side-Effects (Abstract), Arthritis and Rheufatism 7: 300, 1964.

In a double-blind non-crossover study in 33 patients (31 rheumatoid arthritis, 2 rheumatoid spondylitis) using indomethacin and placebo, the drug was shown to be significantly effective on subjective and objective parameters.

Hart, F. D. and Boardman, P. L.: Indomethacin and Phenylbutazone: A Comparison. Brit. Med. J. 2 :1281, 1965.

A double-blind crossover study using indomethacin and phenylbutazone (4 wks. on each drug) in 26 patients with rheumatoid arthritis revealed no significant differences between the drugs with regard to relief of symptoms but a greater reduction of morning stiffness on phenylbutazone and a greater reduction of joint swelling on indomethacin.

Percy, J. S. et al: Indomethacin in the Treatment of Rheumatic Diseases, Ann. Rheum, Dis. 23 :226, 1965.

A double-blind crossover study in 24 patients using indomethacin and phenylbutazone in patients with rheumatoid arthritis revealed similar response for both drugs subjectively and objectively but more patients expressed a preference for phenylbutazone because of lower incidence of side effects.

Smyth, Charley J.: Indomethacin in Rheumatoid Arthritis. A Comparative Objective Evaluation with Adrenocorticosteroids, Arthritis and Rheumatism. 8 :921, 1965.

In a single-blind crossover study indomethacin was compared with placebo. Comparison was also made with corticosteroids. There were 55 patients with rheumatoid arthritis. Results were measured objectively only (ring size, grip strength, walking time etc.). There was a significant difference between both drugs and the placebo in various parameters (not in all). A comparison of steroid alone against steroid plus indomethacin revealed improvement in certain parameters in the latter group. Indomethacin could be completely substituted for steroids in 16 of 30 patients, and in another 4, steroid dosage could be reduced.

Abrupt substitution of placebo for indomethacin revealed prompt relapse in 3 to 5 days with suppression when indomethacin was restarted. This maneuver and its results were quite obvious in studies done by Rothemich (see below).

Rothermich, N. O.: An Extended Study of Indomethacin. II. Clinical Therapy, J.A.M.A. 195:1102–1106, 1966.

This paper comprises experiences with 216 patients with rheumatoid arthritis (and its variants), rheumatoid spondylitis, gout and miscellaneous conditions. (There were 150 case reports in the NDA; the published paper gives the investigator's additional experiences.) Of particular interest is that 22 patients with rheumatoid arthritis were involved in a double-blind trial with placebo; as stated by the investigator, 20 did better on indomethacin. In addition, single blind placebo substitutions were made in 86 patients with rheumatoid arthritis. In 70 of these was a rapid relapse on placebo. This was verified by repeated trials in 55 patients.

Wanka, J. and Dixon, A. St. J.: Treatment of Osteo-Arthritis of the Hip with Indomethacin. A Controlled Clinical Trial, Ann. Rheuf. Dis. 23:288, 1964.

A double-blind crossover trial involving indomethacin and placebo was performed in 18 patients with osteoarthritis of the hip (4 weeks drug, 4 weeks placebo or vice versa). Indomethacin significantly relieved pain and increased joint motion.

Michotte, L. J. and Wanters, M.: A Clinical Trial of Indomethacin, Rhumatologie 16:447–451, 1964.

Twenty patients with osteoarthritis of the hip were treated for 1 wk. on phenylbutazone followed by 2 wks. on indomethacin, 1 wk. on placebo and 8 wks. on indomethacin. Only objective evaluation (measurement of knee separation) was used. Significant increase in knee separation was noted when patients were switched from phenylbutazone to indomethacin with decrease when placebo was substituted and an increase again when indomethacin was reintroduced.

Additional data in the NDA:

Katz, Pearson and Kennedy performed single-blind placebo-controlled studies in 17 patients. Brown performed brief double-blind crossover studies in 9 patients. Clark performed placebo substitution in some patients (exact number would have to be ascertained by a re-review of the raw data). There was a double-blind placebo-controlled study from abroad by Lapin in 23 patients. He reported a better effect on the drug. The reviewing medical officer found no difference. A number of investigators found that abrupt substitution of placebo for drug caused prompt relapse of symptoms.

Rheumatoid arthritis is one of the most difficult diseases in which to evaluate a drug. Rheumatologists cannot agree on the best clinical design for anti-inflammatory studies. Even the so-called objective techniques used in evaluating results of therapy, such as measuring grip strength and walking time are subject to extraneous factors of the patient's mood, time of day, etc. One cannot always substitute statistical results of a short-term study for long-term follow-up of patients by expert rheumatologists who know their patients. This is not, of course, to imply that controlled studies should not be done. Our recommendations for anti-inflammatory agents include double-blind placebo-controlled and positive-controlled studies for at least 3 months and, in some studies, a cross-over design following a period without drug therapy (or just basic salicylate therapy); we recommend pairing patients, to the degree possible, as to age, duration of disease, severity of disease, sex, response to previous therapy; we recommend evaluation based upon the patient's subjective findings, objective techniques, and ability to withdraw previous therapy. We also recommend that patients be requested to keep a record of their salicylate intake.

We make no claims that this is the best of all possible designs for an anti-inflammatory study. We recognize that designs proposed by others may be shown to have greater validity.

In the application for indomethacin, it was apparent even in uncontrolled studies that many patients with rheumatoid arthritis failed to respond to the drug. Nevertheless, in both controlled and uncontrolled studies, there were patients, unresponsive or only partially responsive to previous therapy, who did respond.

The cause of rheumatoid arthritis is unknown. In temperate countries the incidence among those 15 years of age or older is about 1% for "definite" and 3% for "probable" rheumatoid arthritis. Projecting these figures for the U.S., there may be approximately 1.4 million people over the age of 15 with definite, and another 4.2 million people with probable, rheumatoid arthritis. Among young adults, females are more commonly affected than males but the incidence in the latter rises with age. Many patients became incapacitated. In one study, 58% were unable to engage in their ordinary occupations or household duties.

Rheumatoid arthritis is a systemic inflammatory disease. It is not limited only to the joints but can also involve arteries throughout the body leading to peripheral involvement of the nerves and gangrene of the extremities, and occasionally to a fulfillment, fatal, generalized arterial involvement. It may involve the heart, leading to inflammation of the membrane covering the heart, congestive heart failure, and other heart disturbances. It may involve the lungs. It may involve the eyes. It also is associated with a condition called amyloidosis, which can lead to impairment of heart, liver and kidney function. Rheumatoid arthritis can also be accompanied by enlargement of the spleen with resultant decrease in red and white blood cells and platelets.

Rheumatoid arthritis is characterized by pain, swelling, stiffness, limitation of motion and eventual deformity and destruction of the involved joints, accompanied by fatigue, weight loss, anemia, wasting of muscles, and thinning of the skin, in addition to the possibilities of other organ involvement mentioned previously. At the onset of rheumatoid arthritis it is practically impossible to predict the future course of the disease in the individual patient. It generally follows one of two types—episodic or sustained. Often, the disease will be episodic at the beginning and then become sustained. Episodes may be short-lived, that is, less than a year in duration. Once affected, the joint tends to remain inflamed for weeks, months or years. During an episode a certain degree of irreversible damage occurs. Statistically there are certain laboratory and clinical findings which point to a poorer prognosis but, as indicated above, no definite predictions can be made in an individual case.

The principle drugs available for the treatment of rheumatoid arthritis are few, they are not uniformly effective, and most have very significant and frequent adverse effects. These drugs are:

1. *Salicylates.*—Newly diagnosed patients with rheumatoid arthritis, as well as patients with long-standing disease, are usually treated with salicylates, most commonly aspirin. This may be the sole therapy in those who can tolerate the large doses required and who obtain adequate relief from it or it may be given in addition to other drugs. The minimal dose is 2 tablets four times a day; many patients require 3 or 4 tablets four times a day and some must dose themselves every three or four hours and during the night. The mechanism of action of salicylates involves suppression of inflammation and pain. Common side effects in the dosage required include nausea, vomiting, ringing in the ears, partial deafness, bleeding into the gastrointestinal tract, and ulcers of the stomach or upper intestine which may, in some cases, progress to hemorrhage or perforation. Gastrointestinal intolerance to long-term use of salicylates is a major problem in about 25% of patients. Less common adverse effects include dizziness, headache, and asthma. Occasionally, serious reactions can occur in patients sensitive to aspirin and other salicylates. A few have died after taking as little as one or two tablets of aspirin. Whether or not kidney damage can occur from aspirin alone has not been finally settled.

2. *Phenylbutazone* (trade name Butazolidin) and *oxyphenbutazone* (trade name Tandearil) are widely used in the treatment of rheumatoid arthritis. These drugs affect both pain and inflammation. They are considered by many rheumatologists to have approximately the same degree of efficacy as indomethacin. Like the latter, they are more effective in gout and rheumatoid spondylitis than they are in rheumatoid arthritis. Like other anti-inflammatory drugs they cause adverse reactions in a certain percentage of patients. These have been reported to occur in 23 to 44% of patients in different studies. Adverse reactions most commonly occur in those treated for longer than a week. The occurrence of adverse reactions has an effect on the reported relief obtained from the butazones (as well as from other anti-inflammatory drugs) since in one study, among those who experienced adverse effects, only 16% reported good relief of arthritic symptoms as opposed to 60% relief among those experiencing no adverse effects. Common reactions include retention of salt and water by the body with resultant swelling of the legs and also possible aggravation of pre-existing heart disease because of

water retention. Gastrointestinal reactions (nausea, vomiting, heart burn, etc.) account for about ⅔ of all side effects.

These drugs can also cause or aggravate ulcer of the stomach or upper intestine with resultant hemorrhage or perforation, in some cases. The most feared of the adverse effects is that involving the blood, where depression of bone marrow function can cause severe depression in white cells, red cells and platelets. These can lead to severe, sometimes fatal infection or bleeding, depending upon the elements involved. Leukemia has been reported in some patients treated with phenylbutazone; a cause and effect relationship to leukemia cannot be either included or excluded. Skin rash is a not infrequent occurrence. Occasionally, dizziness, mouth lesions, mental confusion, headache, blurring of vision, impairment of vision, temporary deafness, hepatitis, jaundice, kidney damage and enlarged thyroid have been reported. Their use in conjunction with anticoagulant drugs may result in bleeding, sometimes severe.

3. *Corticosteroids.*—The adrenal corticosteroids, namely cortisone and the newer steroid agents, are widely used in the treatment of rheumatoid arthritis. They are more effective than salicylates, phenylbutazone or indomethacin but the incidence of adverse effects is high and predictable; in general, the adverse effects are directly related to dosage and duration of administration. They consist of mooning of the face, hirsutism, acne, diabetes, thinning of bones with spontaneous fractures, destruction of bone in the hip, arm or fingers, loss of body protein and muscle, imbalance of body sodium, potassium, chloride and calcium with, in some cases retention of salt and water, elevation of blood pressure, bleeding into the skin, insomnia, mental disturbances, blood clots (sometimes fatal), ulcers in the stomach or upper intestine with, on occasion, hemorrhage of perforation, cataracts, laucoma, inflammation of the pancreas, inflammation of the blood vessels, convulsions, masking of infection so that it goes untreated, aggravation of existing infection, including tuberculosis. The corticosteroids depress the adrenal glands so that particular care is required during periods of stress, such as infection or surgery, for up to two years after the corticosteroids are withdrawn. There are, in addition, other less serious side effects.

4. *Chloroquines.*—Chloroquines are another group of drugs used for the treatment of rheumatoid arthritis. Their mechanism of action in this disease is unclear. Improvement in symptoms usually does not appear until these drugs are taken for three to six months. Adverse effects consist of skin rash, loss of hair, nerve damage including deafness, gastrointestinal symptoms of nausea, vomiting, diarrhea, headache, dizziness, emotional disturbances including psychosis, convulsions, and muscle weakness. Some cases of depression of white blood cells have been reported. The most feared adverse reaction involves the eye. Both the cornea and the retina have been involved with resultant impaired vision. Involvement of the retina is frequently irreversible and, since the lesions often progress after the drug is withdrawn, this involvement may lead to blindness. Frequent eye examinations are required in patients on these drugs and they must be withdrawn at the first sign of visual disturbance.

5. *Gold Salts.*—Gold salts are another group of agents frequently used in rheumatoid arthritis. Their mechanism of action is not known. Adverse effects occur in 14 to 62% of patients reported in the literature (the average in a large group was 32%). These reactions consist of a large variety of skin rashes, hair loss, baldness, mouth lesions, kidney damage, depression of the bone marrow with decrease in red and/or white cells and platelets. Occasionally, nausea, vomiting, diarrhea, severe ulcerations of the small and large bowel and hepatitis have occurred. Peripheral nerve damage, bronchitis and other side effects occur occasionally. The incidence of "severe" adverse effects is about 5%. Fatalities from gold salts were as high as 3% when they were first introduced but now the mortality is placed at less than 0.4%.

Taking into account the drugs that were available in 1965 for the patient with rheumatoid arthritis, bearing in mind the limitations of this therapy and the hazards that were encountered in their use, we concluded that there were sufficient data from adequate, controlled studies to support the conclusion that indomethacin would be safe and effective for some patients with rheumatoid arthritis.

The labeling contained enough information on effectiveness and adverse reactions to enable the physician to utilize his professional judgment in selecting the patients who would be expected to benefit from this medication. These patients would be those who had obtained little or no relief from salicylates or other agents. They would be patients who had experienced adverse reactions to other agents. They would be patients in whom it was considered desirable to attempt to substitute indomethacin for other agents (or decrease the dose of other agents) to reduce the possibility of adverse reactions to the other drugs. They would be patients in whom it was considered desirable to use a drug which did not produce some of the serious side effects of other available drugs. On that basis, the New Drug Application was approved. Our final evaluation was that indomethacin could be approved for use in rheumatoid arthritis, acute and chronic gout, rheumatoid spondylitis, and osteoarthritis of the hip.

The drug is effective only for the control of inflammation and pain in selected patients. Its therapeutic index, that is, the ratio of desirable effects to undesirable effects, places the drug in the middle of the spectrum of drugs used in the treatment of rheumatoid arthritis. The *ultimate* drug for the treatment of this disease has not yet been identified.

As with all drugs used in the management of rheumatoid arthritis, more extensive clinical experience has revealed new hazards and has further defined the conditions of expected effectiveness for indomethacin. Dr. Jennings is here to present the experience with, and the handling of the drug, since its approval for marketing.

Thank you, Mr. Chairman, for the opportunity to appear today. I will be happy to answer any questions you may have.

Senator NELSON. On the question of IND's, as you testified earlier, under the present circumstances you rely exclusively on evidence submitted by the company to evaluate the safety and efficacy of a drug. We had some testimony last week on this point. What would your viewpoint be about establishing a third independent party, perhaps an agency, similar to the Cooperating Clinics Committee of the American Rheumatism Association, which is funded by the NIH to evaluate drugs. In other words, in addition to the experimental work submitted in the IND by the company, you would have as a kind of standard of measurement, the results of studies done by a completely independent group such as the cooperating clinics committee. Would you consider that to be a valuable addition to the information for you to have at hand at the time you evaluate an NDA?

Dr. HODGES. If we take into account the quite formidable obstacles to setting up such an institute, such as obtaining money, place and people, qualified people, and patients, which obviously you have to overcome, I would feel that such an institute would serve an extremely useful purpose both for testing drugs before approval, and I think even more important for the testing of these drugs that have already been marketed. The bulk of drugs are on the market, obviously—there are at least 3,000 of them at the National Academy of Science review. There is a vast number of new drugs coming on the market. So I think we might pin that down, testing marketed new drugs that we have a reason for, for efficacy and toxicity, and for confirming, only for confirming, evidence submitted in New Drug Applications, such an institute certainly has a place.

Senator NELSON. Well, the Cooperating Clinic Committee of the American Rheumatism Association conducts these kinds of studies. And they are connected with hospitals. For example, if they want a double-blind study of some kind they can contract, and do, I guess, with various hospitals to do it. Is there any reason why that method wouldn't be practical in your view?

Dr. HODGES. There are a number of instances in which it is not completely satisfactory. Very often the numbers of patients in each of the cooperative clinics is small. These are a large number of observers—they may be highly qualified people, they may be just fellows, or senior residents just finishing their training—these are drawbacks to a cooperative type of program. It is applicable to some drugs, but certainly not to all.

Senator NELSON. What I am getting at is, what you have now is just a total reliance upon the information which the company, which has an interest, of course, in promoting the drugs, furnishes to you. I am asking, isn't there some method that you could establish of testing drugs yourself, either in FDA facilities or at NIH or any independent organization. It just seems to me that there ought to be some way of assuring that quality testing is being done, and some standard of measurement against which the companies would know how their test results compared.

Dr. HODGES. I am of course infringing upon policy matters, which are in the province of the Commissioner of the Food and Drugs. But I think I can give you a personal opinion. I think this is an end toward which we should be moving. But I would like to make it clear that that is really a personal opinion, and does not reflect official agency position.

Mr. GOODRICH. May I say one thing on that, Senator?

Senator NELSON. Yes.

Mr. GOODRICH. The impression seems to be that most of the material submitted in the New Drug Application is research conducted by the company itself. It is generally not true. Most of the research in the New Drug Applications, certainly most of the good research, comes from the academic community, and from a variety of sources engaged in investigation. Under the IND the company is required to identify the type of investigation necessary to prove the safety and effectiveness, and to identify these investigators with proper settings, proper background, and proper training, that can carry this out. So a New Drug Application, to be approvable, should contain a variety of experiences from well-qualified investigators at different points of view to validate the claims. And this is basically what we are driving for in all the New Drug Applications now. We are not relying on research done in the company's own resources—would you say 10 percent of the time?

Dr. HODGES. It is not 10 percent. The only research that is done to any extent by the companies really is the very beginning, developing the drug in the laboratory, developing that it is safe to give it to human beings. And from there on it is of course contracted out, just as in the case of all of the investigators that you mentioned today. Their only connection with the company was that they were doing the studies for them.

Senator NELSON. Isn't it correct that a number of scientists and doctors do continuous studies for drug companies?

Dr. HODGES. That is correct.

Senator NELSON. For a period of years?

Dr. HODGES. That is right.

Senator NELSON. And that the company tells them what to do, and the company pays for the study. Are you satisfied in matters as important as this to rely upon such studies and do you feel sure that there would be no bias?

Dr. HODGES. We inspected a number of the people who do a large number of studies, for usually more than one firm. They are in the business. And we find that their quality is quite variable. At one extreme there was an investigator whose data were so unacceptable that we would refuse to accept anything from that individual. At the other end of the scale we have inspected an investigator who does this, and our M.D. went out and looked thoroughly into it, and was quite impressed with the thoroughness of what he was doing.

I agree, he is doing it on contract. The firm generally will give him the drug and say the type of study that they want carried out. They are paying him to do the study. This is an ethical position, of integrity, and I think there is nothing wrong with it.

Senator NELSON. I am saying, in a matter as important as this you are relying solely upon data furnished by a company that paid for the data to be gathered. It may be the best in the world, but on the other hand you have nothing to measure it against. And, further, it might be on some occasions the worst in the world, and you could have a calamity as a result.

Dr. HODGES. This is why we require many studies from many investigators, one of the reasons. The other is to make sure that we don't get a good result just by coincidence, by accident in one study. We require a large number of studies by well-qualified investigators. In this way we hope to eliminate the possibility that the application is based on poor data.

I would also say that we do, though not very often, go out and actually visit the investigators—without any idea that they are doing anything wrong, but just to get their direct impression of the drug and see what the work was like that they did.

Also, Senator, we don't just accept a summary from the investigator. We expect from him and require by law everything that he has pertaining to that patient in that investigation. And so this is why the applications are so voluminous. But we certainly have everything available to us that the investigator has available to him as far as data are concerned.

Mr. GROSSMAN. Doctor, may I just ask you in this area—Senator Nelson asked you if you were satisfied. And I don't quite know what your answer to that was. I have just made a few notes on some of the statements you made about moving toward improvement, the quality of the research is variable. And you talked about masses of material being submitted to you. And I remember you said something about 170-odd people that were available to you to do this amount of work. I just don't know whether you could possibly be satisfied. I don't see how the system can possibly work and why you can't come up and tell us what recommendations you have specifically to improve the system. This system does not seem to be the very best. And you have said that yourself.

Dr. HODGES. There is room for improvement.

Mr. GROSSMAN. There is always room for improvement. But what are we doing today to improve it so that it will be better tomorrow? I don't really see anything. We have talked about the companies who have research and who have submitted it to you, and these companies are, in effect, hiring people to do the research. Now, I find it hard to see how this is interpreted as being objective over a long period of time. It may be that this is the best system that we can come up with.

But I don't see anybody coming up and saying we have looked at this and thought about it, and we have ruled all these things out for various reasons.

Dr. HODGES. Well, we have taken a number of steps in the Office of New Drugs of the Bureau of Medicine. I mentioned earlier just the simple quality of the applications that were submitted.

Mr. GROSSMAN. You mentioned the volume and the mass of material, and I wonder how 170 people can really objectively make an independent study of all this material.

Dr. HODGES. Well, they do; they look at every page of every submission. We have to. I think that we are doing—we are trying to change our system somewhat to try to make greater use of computers to eliminate some of the spadework. But we are still going to have to do a substantial amount of looking at the hard data ourselves.

Mr. GROSSMAN. Do you think you could submit to the committee specifically what you are doing, and what you have done, and what you think should be done? I just think it is time we found out what changes are to be made, and what you recommend, and what you rule out. Is that possible? I don't want to take the time from the 170 people to do that.

Dr. HODGES. We each year sit down, or more often than that, but once a year we sit down and make out a report which shows our plans for the next 2 years and the next 3 years, what we can try to do to process the New Drug Applications, and what we can do to try to improve the quality of the reports submitted. I shall be happy to submit the report to you from the Office of New Drugs. I shall welcome any comments you have on it.

Mr. GROSSMAN. Thank you.

Mr. GOODRICH. I can summarize the major things that have been done since the passage of the Kefauver-Harris amendments in 1963. The IND provisions were put into effect promptly. We processed the great bulk of the applications that came in in May and June. We became current with that operation, as Dr. Hodges has indicated. We reorganized our Bureau of Medicine to more adequately handle this kind of an operation, so that our physician specialties would be brought to bear on special problems. We improved the recordkeeping and the reporting provisions that were in the Kefauver-Harris drug amendments. We have contracted for complete review of the efficacy of all claims on drugs approved in the past. We have revised the New Drug Application form to make the companies submit it in a more orderly and a more definitive form: that is, to have companies' data organized better, to have the companies present a thoughtful and proper analysis of their own data, so that that would simplify the operations of our reviewers. And we have, as Dr. Goddard himself has stressed, and only within the last month, urged the companies to concentrate more on quality and less on numbers, with the idea of improving the clinical investigations that are going on.

Mr. GROSSMAN. That is very helpful. And I think that is all to the good and the credit of the FDA. At the same time I think it aims at correcting the system that exists. And I think sometimes you should stop and think, in correcting something, should we be dealing in this same system.

Mr. GOODRICH. Those are all brought about, as you know, with the enactment in 1962 of basic changes in the law under which we operate. We have in the spirit of that act attempted, and we are still attempting, we think successfully, to carry forth the will of the Congress. Now, there are going to be instances where judgments about the performance differ, and we are not always satisfied with our own behavior in this respect. But we do strive for improvement, and we welcome a review of this sort that will emphasize the need for looking more critically at some of these areas.

Mr. GROSSMAN. At the broader areas?

Mr. GOODRICH. Yes, sir.

Mr. GROSSMAN. Thank you.

Senator NELSON. Dr. Hodges and Dr. Finkel, I appreciate very much your taking your time to come here today to give your testimony.

Thank you very much.

(The supplemental information submitted by Mr. Gordon follows:)

CORRESPONDENCE BETWEEN THE MERCK COMPANY AND ITS INVESTIGATORS ABOUT INDOCIN

UNIVERSITY OF OREGON MEDICAL SCHOOL,
DEPARTMENT OF PHARMACOLOGY,
Portland, Oreg., February 25, 1964.

Dr. NELSON H. REAVEY CANTWELL,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DOCTOR CANTWELL: Herewith are the special case reports for 11 cases who have had trial of the "Indocin" capsules. The number of the cases are from 3518 to 3528. For the record, I am retaining the additional case record forms that you sent and numbered from 3529 to 3567. These unused forms will be used for any additional cases that are placed on "Indocin" capsules. However, if you wish these blank case forms returned, I can do that.

As you know, I sent you a copy of the individual case records for all the patients (21 cases) who have received both the tablets and the capsules of "Indocin". I am currently writing this up as a short report for possible publication as a research note in Current Therapeutic Research. When I complete this short note, I shall forward you a copy for your inspection.

I hope that your case reports for the capsules are coming in satisfactorily and you can get off the material to the FDA. Good Luck!

With best wishes,

NORMAN A. DAVID, M.D.,
Professor of Pharmacology.

MINNEAPOLIS, MINN., *July 9, 1962.*

NELSON H. REAVEY CANTWELL, M.D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: I have made a preliminary analysis of 50 patients with rheumatoid arthritis who have received MK–615 for at least one week. As I am sure it will take some time before I can complete the clinical evaluation forms on each patient, I thought you might be interested in my impression of the drug at this time.

Of the 50 patients 22 recorded no help or else obtained the same degree of help as from the placebo.

Nineteen patients recorded slight help in the range of 10 to 25 percent improvement.

Eight patients reported significant help which I quantitated, at 25 to 50 percent relief of symptoms.

One patient reported great help, that is, more than 50 percent improvement. Eleven patients who were on medication for at least 3 weeks had the laboratory data which you suggested:

There was no evidence of new ulceration or aggravation of previous X-ray findings of the upper G.I. tract.

Urinary tract disturbance was evident in 4 patients: One had a transient 4 plus albuminuria and 3 showed a few casts. One of these patients who is severely hypertensive had a BUN of 36 which fell to 30 two weeks after stopping the MK615; no prior BUN was recorded.

Some evidence of liver function disturbance appeared in 7 of these 11 patients: The BSP was elevated in 4; the Cephalin floc was 3 or 4 plus in 5 patients; the alktase was elevated in 4. Unfortunately I did not do base line values in most of these patients, therefore it is impossible to say if these were the result of this medication in as much as most of these patients were on other drugs such as small doses of steroids, gold, chloroquin or were recently on Butazolidin. However, one patient might be worth indicating in detail and I have enclosed this work sheet that was filled out by Dr. Schultz at the University. One other patient had a normal ceph floc before therapy.

The symptomatic disturbances were relatively minor: One patient reported nausea after a single 10 mg. dose, repeated on 2 occasions; one patient said her stools were somewhat loose while on the medication for one month; One patient reported mild itching and arythema with 2 trials of the drug (75 mg. a day for 3 days and again on 30 mg. for one week); three patients were slightly stimulated mentally and event felt a little jittery on the medication.

What this all adds up to is difficult to say. Certainly many of the patients were greatful for the added relief the medication seemed to offer even if it was not in the great degree such as with steroids. The apparent evidence of hepatic change might be a cause of concern. I would appreciate your ideas concerning extending this study or changing the procedure. I am just about out of the medication and will conclude the study if you wish.

I am enclosing some statements from the laboratories where the test procedures were done on these patients. There may still be a few coming in yet so I will send them later.

Sincerely,

PAUL J. BILKA, M.D.

MINNEAPOLIS, MINN., *August 29, 1962.*

NELSON H. REAVEY CANTWELL, M.D.
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: During the last month I have been carrying on a new trial with MK–615 using the higher dosage range which you suggested. A preliminary analysis of 22 patients indicates rather significant improvement in the results using this higher dosage. All patients have rheumatoid arthritis, and the majority have been on the lower dosage trial. The results after 2 to 4 weeks therapy are as follows:

Four-patients report no significant improvement.
Five patients report 10 to 25 percent subjective improvement.
Twelve patients report 25 to 50 percent improvement.
One patient reports marked, or over 50 percent improvement.

There have been 2 complaints of nausea caused by the higher dosage and one patient who had a previous active duodenal ulcer, and also is on 0.6 mg. beta dexamethasone per day developed an active DU on 100 mg. MK–615 per day. One other patient complained of headaches. I have not, as yet analyzed the laboratory data, but will do this shortly when I fill out the regular investigative forms. I thought, however, that you would be interested in these preliminary findings.

Sincerely,

PAUL J. BILKA, M.D.

STATE UNIVERSITY OF IOWA,
Iowa City, Iowa, April 18, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: I received your letter this morning and want to thank you for suggesting a grant for the rheumatology section at the University of Iowa.

Since you were here, we have started a number of new patients on indomethacin (the LX capsules). At least three of the patients complained of severe epigastic distress within 30 minutes after taking the capsule. Therefore, in the next few subjects we started them out on 1 capsule twice a day increasing 1 capsule daily until they reached the maximum 6 capsules and believe it or not we encountered no distress. This is the method we will follow for the time being, with our fingers crossed.

The fifteen year old patient with generalized psoriasis and psoriatic arthritis returned for a check-up and is under excellent control on a total dose of 150 mg. per day. She goes to school daily and is able to walk much better than she has at any time during the past year. Another woman (age 45) was admitted with generalized psoriasis and psoriatic arthritis. Before she was admitted to the hospital she was started on terrific doses of steroids which did not control either the painful hands or the skin eruption. The dermatologist started her on 42 mg. Triamcinelone and a few days later we began the indomethacin, 2 tablets at first then increasing daily until she reached the maximum of 300 mg. By the time that we reached the maximum dose she had little or no pain in her hands, was able to make a partial fist and began to feel much better. This morning we have her down to 16 mg. Triamcinelone. She is able to be up and about, has no fever, the skin lesion is receding rapidly and she can actually close her fingers and grasp objects. We started another psoriatic arthritic who has been on steroids for over five years to determine whether or not we can reduce the steroid dose.

Under separate cover I am sending you another batch of the monthly Bulletins in case you need some of these. I have had several calls from Iowa physicians asking me about the drug and two of them have sent patients to us so that we could evaluate them and give them indomethacin.

Again I want to thank you for your kindness and will see you in June.

Sincerely yours,

W. D. PAUL, M.D.

SCRIPPS CLINIC AND RESEARCH FOUNDATION,
La Jolla, Calif., April 29, 1963.

ELMER ALPERT, M.D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. ALPERT: I thought I would drop you a little progress note as to what we are doing with the MK–615 that you sent to us, and at the same time, ask if you could send me some more.

With the full realization that our clinic material is too limited in numbers for a large double blind study, we have been merely using MK–615 in the management of some of our patients and recording our impressions of it. Today I can merely tell you that we have seen no untoward effects from it although our top dose has been only 250 mgs. as per your suggestion. We have also found that patients tolerate MK–615 together with ASA dose of 4 grams a day without signs of salicylate intoxication. I can also say that the persons on MK–615 seem to be doing quite well although it does not seem to be holding one 40-year-old lady.

Finally, regarding our equilibrium dialysis study with MK–615 we have found that MK–615 does, indeed, bind to the same site on albumin that is bound by the I^{131} labeled Urokon. As you recall, sodium salicylate also binds to this site but we think that MK–615 has a stronger bond than does sodium salcylate.

Meantime, with your generosity I would greatly appreciate some more 50 mg. MK–615 tablets so that we may continue our few patients on it.

Very sincerely yours,

RICHARD S. FARR, M.D.,
Head, Division of Allergy and Immunology.

MINNEAPOLIS, MINN., *May 8, 1963.*

NELSON H. REAVEY CANTWELL, M.D.,
Merck Sharp & Dohme Laboratories,
West Point, Pa.

DEAR NELSON: I have decided to make a preliminary analysis of the patients on the Indocin tablets. Since I started the higher dosage schedule, beginning last summer, there are 63 patients who have been treated from up to eight months, and it certainly looks like we are getting a better result using the minimum dosage of 100 mg. a day, with the vast majority getting 150 mg. per day as the minimal dosage.

15 patients had no help.

17 patients recorded slight help (that is less than 25%).
20 patients had significant help (25 to 50%).
11 patients report great improvement (over 50%).

I have not yet analyzed all of the laboratory data, so I can not give an accurate statement as yet, however certain things are apparent and might be of interest at this time:

18 patients reported severe headache; all but six were able to continue the medication at lower dosage levels or by adding Benadryl; 8 patients reported severe gastro intestinal upset.

One patient (Mr. Jensen) had a history of a DU, but the pretest X-ray was negative. During the third month of 200 mg. per day, he developed an active DU. He was continued on the medication in the same dosage and X-rays two and four months later show the ulcer healed.

Another patient (Mrs. Rose) with a known active DU was started on Indocin 150 mg. per day and was continued on this for two months because of the marked relief she obtained. At this time however, her GI symptoms increased, the X-ray showed the still active DU and the Indocin was stopped.

A third patient (Mr. Rardin) with a known history of a DU and with signs of activity was given a two month trial of Indocrin 75 mg. per day. His ulcer symptoms also increased on the medication and the X-ray showed an active DU. All of the other patients had negative X-rays.

I will start going over the charts for the detailed analysis of the laboratory data and will let you know of the results. The work with MK715 is too early to make any comments on except that it seems at least as potent as 615 in the two to one dosage ratio.

I am enclosing the laboratory charges for March and April. Again would you have this made out to St. Barnabas Hospital, Arthritis Research.

I shall soon be enlarging the facilities for out-patient care at the Kenny Institute and we will be in a position to utilize extra funds for our project there. If Merck can make an additional contribution of $3,000 toward this work, it will be useful and appreciated.

Sincerely,

PAUL J. BILKA, M.D.

MINNEAPOLIS, MINN., *June 24, 1963.*

NELSON R. CANTWELL, M.D.
Merck Sharp & Dohme Laboratories,
West Point, Pa.

DEAR NELSON: I have gone over the data on the 63 patients I reported to you earlier this month and have extracted the information you recently asked about.

1. 40 patients have been on 150 mg. or less of Indocin per day. 20 of these reported no or slight help and 20 reported significant (25% to 50%) or great (more than 50%) help.
2. 15 patients had 200 mg. per day and 7 reported no or slight help and 8 reported significant to great help.
3. 8 patients had more than 200 mg. per day. 5 reported no or slight help and 3 reported significant or great help.
4. All patients had rheumatoid arthritis.
5. There was a definite increase in GI symptoms and especially headache with increase in dosage. There was very little headache on 100 mg. or less per day. Gastric irritation seems to be an increasing problem.
6. I have had little experience with non-rheumatoids so far, but 1 patient with Reiter's disease had an excellent response; 1 patient with chronic gout had a good response and 1 patient with Scleroderma had slight help.
7. Regarding headache and migraine; the very day you called, the first patient I asked the question of stated that she had been a frequent sufferer of migraine before developing her arthritis. She had been free of headache until it recurred with Indocin. However, she stated this headache was different from what she remembered her migraine was like. I haven't had the opportunity to put the question to all patients, but several have denied previous migraine, yet 3 have admitted to prior migraine.
8. 39 of the 63 patients have been on Indocin for 2 months or more, some over 8 months. It is my plan to carry as many on long-term therapy as tolerate and benefit from the drug. New patients are being constantly added as I presume is your desire.

Sincerely,

PAUL J. BILKA, M.D.

CLEVELAND METROPOLITAN GENERAL HOSPITAL,
Cleveland, Ohio, June 27, 1963.

NELSON H. REAVEY CANTWELL, M.D.,
Merck Sharp & Dohme, Research Laboratory,
West Point, Pa.

DEAR DOCTOR CANTWELL: This is in answer to our telephone conversation. As I mentioned to you in my letter of 26 January, we have treated 51 patients with acute rheumatic fever. I have discussed the whole situation with Dr. Mortimer and our plans for analysis are as follows. Dr. Mortimer is presently analyzing the data and in September Dr. Correa, who participated in the study in Chile, will come to the United States to spend six weeks here going over the data and preparing it for publication. It is possible that we will have a rough draft before that time and if we do we will forward it on to you. In addition, Dr. Correa is going to bring with him the serum specimens that we collect once a month from these individuals. In October I am going to Chile to collect further specimens from the study group. The final analysis of the effect of the drug on valvular heart disease will be completed in January. One of the problems that we will face will be adding the final evaluation of the effect of the drug on valvular heart disease to the analysis of the effect of the drug on the acute phase symptoms. It is my feeling that the two should go together since there is no indication that the drug would or should be effective on valvular heart disease and it is not likely that a second publication will be justified. We are in the process of training two technicians to help us complete the laboratory work.

In going over our financial situation, we will require the money remaining in the original proposed budget to complete this work in an adequate fashion.

With best personal regards.

Sincerely yours,

CHARLES H. RAMMELKAMP, M.D.,
Professor of Medicine.

DUKE UNIVERSITY MEDICAL CENTER,
Durham, N.C., July 9, 1963.

Dr. NELSON H. REAVEY CANTWELL,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: I enclose your completed questionnaire with an attached sheet listing a few further observations. We do not plan on making any further formal report of our findings this year. The protocol sheets are available to you at any time, of course. I would emphasize as I did prior to accepting MK615 for use that the data here are in no way to be interpreted as representing a controlled study. Our patients come from distant towns usually and are often under the simultaneous care of a local physician whose prescriptions are seldom known to us. We simply report what we have noted in our particular and transitory clinic setting.

We need a further supply of both 25 mg. and 50 mg. capsules of MK615, if these are available. I share with you and impression that these are well tolerated.

Sincerely yours,

GRACE P. KERBY, M.D.,
Rheumatism Clinic.

STANFORD UNIVERSITY SCHOOL OF MEDICINE,
Palo Alto, Calif., August 22, 1963.

NELSON H. REAVEY CANTWELL, M.D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: I am sorry I haven't answered your previous request for information about Indomethacin. For various reasons I have not put our results together yet but will do so in the not too distant future. This was our first effort at drug evaluation, and I am afraid we have been somewhat inefficient in maintaining precise up-to-date evaluations of the patients. Though all the necessary information is in their charts, we have not extracted it all as yet.

Our impression of the drug remains good It is clearly not the answer to rheumatoid arthritis and has not been helpful in those few instances of connective tissue disease where we have tried it: but in a significant number of patients it is of decisive benefit when other medications have failed.

I am writing to you about a financial question. We have obtained a modest amount of laboratory information on our patients which the patients were guaranteed would not be charged to them. The day of reckoning is approaching with the hospital when they insist that I settle accounts. I am therefore writing to ask what mechanism you would propose that we employ to obtain the money from you to meet these expenses?

Many thanks for your consideration.

Sincerely,

HALSTED R. HOLMAN, M.D.

UNIVERSITY OF UTAH,
COLLEGE OF MEDICINE,
Salt Lake City, Utah, October 15, 1963.

DR. NELSON H. REAVEY CANTWELL,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR NELSON: It was pleasant to meet with you again and learn first hand of the current status of MK615. Your offer of assistance in the statistical analysis of our data is greatly appreciated. The data summary sheets are completed and will be forwarded to you under separate cover, along with detailed information as to the method of acquiring and computing the scores on each patient. The relative weight of each parameter will be described. For your information and use, we are submitting a summary of our experiences with indomethacin in a double blind crossover and long-term evaluation study. All of the patients included in the double blind study fulfilled the following criteria:

(1) A diagnosis of either definite or classical rheumatoid arthritis, using the A.R.A. classification.

(2) Active disease as evidenced by swelling and tenderness and/or the necessity of corticosteroids to control symptoms.

Most of the patients have had moderate to severe disease with continuous activity for greater than five years. The patients were paired as closely as possible in regard to age, sex, duration of disease, severity of disease and stage and class of disease. One of each pair, chosen at random, was started on indomethacin, with the other member of the pair being started on placebo. This was done in such a way that neither the patient nor anyone involved in the evaluation of the patient's response knew which medication the patient was receiving at any time. All patients were started on a dose of 200 mg. a day in four divided doses. At the end of one month, the parameters for evaluation were measured again and the other form of the drug given. After one month on placebo and one month on indomethacin, all patients were started on known drug for the long-term evaluation. All of the examinations were repeated at monthly intervals, or as close thereto as possible. With the long-term evaluation, dosage of indomethacin was varied according to the patient's response and/or side effects.

The following parameters of disease activity were evaluated at each visit. The patient's evaluation of the amount of pain he had had in the previous month, graded on a scale of no pain, slight pain, moderate or severe pain. The number of aspirin taken; the duration of morning stiffness; the amount of corticosteroids or other medication. A cuff compression test of hand grip and a ring size of each finger were taken each visit. Swelling and tenderness of the shoulders, elbows, wrists, fingers, toes, ankles, knees and hips were evaluated according to the following scales: swelling was graded 1 for slight synovial thickening; 2 for swelling that changed the contour of the joint; 3 was swelling that obliterated the normal joint contour; 4 was the presence of a demonstrable effusion. Tenderness was graded 1 for the patient says it hurts when pressure is applied; 2, the patient says it hurts and winces; 3, the patient tries to withdraw from the stimulus. It was possible for the same observer to evaluate the patients greater than 90% of the time. Sub-totals of the swelling, the tenderness, the grip strength, the ring size, the duration of morning stiffness, the amount of pain, the number of aspirin and the milligrams of prednisone or equivalent were obtained for each visit. The difference between the individual parameters and its base line was obtained so that a negative score indicated worsening of the arthritis, whereas a positive score indicated improvement. In the parameters of swelling, tenderness and number of aspirin (300 mg. tablets) a change of 1 was reflected as a change of 1 in the score. A change in the amount of prednisone was scored as the number of milligrams times two. The duration of morning stiffness, a change of ½ hour was scored as a change of 1. The grip strength was scored as the change in total score of both hands divided to 20, or in other words, a change of 20 mm. of mercury was scored as a change of 1. The sub-totals of the changes in each parameter were then totalled to determine a numerical figure for improvement or worsening of the arthritis. By inspection of the changes in the total score of arthritis, we have evaluated the response to indomethacin as good, fair and none. A good response was considered a response of clearly significant improvement, while on indomethacin, with little or no response while on placebo. A grade of fair was given when there was moderate but definite improvement while on indomethacin, again with little or no response to placebo. The grade none represents either worsening of the arthritis while on indomethacin, or no difference between response to placebo and indomethacin.

We had 31 patients who started the double blind study. Of these, 4 were unable to complete the double blind part of the study because of uncontrollable side effects. The side effects requiring cessation of the study were nausea, vomiting and headache in 2 patients; nausea and headache in 1 patient; and dizziness with nausea and headache in 1 patient. Thus, in the short-term double blind experiment, 68% of the patients had a favorable response; 19% had no demonstrable response; and only 13% had side effects requiring stopping the medication.

The long-term evaluation study has now been under way for ten months, with observations on patients ranging from seven months to ten months in length.

Of the 27 patients finishing the double blind part of the study, 2 were withdrawn before long-term evaluation could be done. One of these was for side effects of the drug, specifically nausea and vomiting, and one patient with a history of bronchial asthma expired with an episode of asthma refractory to all treatment. Of the 25 patients left in the study, 15 had a good response; 9 had a fair response; and 1 showed no response. Of this group, 8 patients have had to stop taking "Indocin" because of side effects that exceeded the benefit they were receiving. These side effects were dizziness in 5 patients; nausea and dizziness in 1 patient; severe refractory ulcer-type symptoms in 1 patient; giddiness and mental fuzziness in another.

In addition to the double blind study, we have used "Indocin" in 12 additional patients. Two of these patients had progressive systemic sclerosis; 1 has the fibrositis syndrome; and 1 has an unusual form of hereditary degenerative joint disease. The remaining 8 patients have a diagnosis of either definite or classical rheumatoid arthritis, and were started on the known drug because of severity of the disease process. Four of these were hospitalized because of their arthritis at the time "Indocin" was started. Of this group, we have had a good response in 9 patients; a fair response in 2; and 1 patient had side effects that required cessation of the drug before any effect could be noted. Of this group, 5 patients have required stopping "Indocin" because of side effects, even though the response had been fair or good.

In our work with "Indocin", we have found that headache, while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduction in dosage of "Indocin". The dizziness, nausea and vomiting, however, have been refractory to most efforts at control with the exception of stopping "Indocin". Using antacids, anti-emetics, etc. has had no effect in stopping this complication. We have found in a few patients that stopping the drug for a period of time, and then re-starting it, has been successful. We have made frequent checks of blood chemistry and hematological studies, and have found no disturbance with hematopoesis or hepatic or renal toxicity. We have had several patients on "Indocin" develop peptic ulcer disease, and have had two episodes of massive upper G.I. bleeding. However, in the 2 patients with upper G.I. bleeding, "Indocin" has been continued after their acute episode and these patients are now 9 months and 4 months post-hemorrhage with no symptoms, or only minimal symptoms remaining. All of the patients who have developed ulcers have also been on corticosteroids.

The possibility of obtaining fewer side effects with as good or better results from the use of the capsule form of 'Indocin' has been of interest to us. As we discussed with you, we would be anxious to try the capsules also in a double blind crossover fashion, similar to our study with the tablet form. To run such a study with the number of patients we would have available would require 90 bottles of 25 mg. "Indocin" capsules, and 90 bottles of placebo capsules. Anticipating the number of patients who will respond favorably to this, and in whom we would like to continue the capsules past the double blind study, we would need approximately 400 bottles of 25 mg. capsules to carry these patients for a total of six months. We feel that there would be certain other studies that should be pursued in the use of "Indocin". These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attempt to correlate electroencephalographic findings with blood level and with effect should be done. We would like to receive some of the bulk "Indocin" so that its effect in experimental models of arthritis could be pursued shortly. Ultimately, the determination of "Indocin's" place in the therapeutic armamentarium of the rheumatologist should be done. Several of these things will require more detailed planning before they can be accomplished. However, the capsule double blind study and use of the bulk drug in experimental models of arthritis could be accomplished as soon as we can receive the necessary drug.

From our experience with your drug "Indocin", we feel that you have developed an agent that has a definite place in the treatment of rheumatoid arthritis, even though we have had considerable disappointment in the amount of side effects. We would feel that with further work, maybe the difficulties might reasonably be expected to be overcome. Although it is still too early to tell, we have noticed in 4 or 5 patients, a tendency for the development of remission of their disease activity. Whether they are truly going into remission remains to be seen, but the evidence suggesting that they are is there.

We can discuss the necessary financial support for a double blind study using capsules when the decision is reached to initiate the study.

Very truly yours,

John R. Ward, M.D.

Duke University Medical Center,
Durham, N.C., December 8, 1963.

Dr. Nelson H. Reavey Cantwell,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

Dear Dr. Cantwell: I am sorry to have missed seeing you at the recent Boston meeting. However I do want to mention two patients in regard to Indocin, one for your own information and one to raise a question re contraindication to use of Indocin.

A 19 year old CF with unequivocal SLE manifesting most strikingly as acute nephritis with good renal function was admitted in October while I was out of town. Because she was not sufficiently critically ill to require immediate ACTH or steriods, my colleagues started her on Indocin, 50 mg per day increasing over about one week to 150 mg per day, at which time I first saw her on return to town. An originally normal BUN rose slightly in the first few days and then to 47 mg percent by the time I first saw her. On the chance that this was the phenomenon you have noted with Indocin in the presence of pre-existing renal disease, Indocin was discontinued. The BUN returned to normal over the next few days.

A young WM with chronic rheumatoid arthritis, on phenylbutazone, was admitted recently to the V.A. hospital here with GI symptoms. Two gastric ulcers near the cardia were demonstrated. He was to be discharged this past weekend with ulcers healing well and promptly, to come to the Rheumatism Clinic at Duke for the first time either this Thursday Nov. 12 or Nov. 19, referred specifically for Indocin. However, recalling the report at the June meeting of patients with previous peptic ulcer/developing multiple gastric ulcers, I question whether Indocin may not be contraindicated in this patient. If it is at all possible to have your comments on any further information concerning the GI tract during Indocin therapy prior to this patient's scheduled first visit to the clinic, I shall most appreciate having them. He has to travel 150 miles from his home, doing his own driving despite severe rheumatoid arthritis. Had I realized that I would be unable to get your comments in Boston, I would not have suggested such an early appointment for the patient.

Following our recent telephone conversation, I sought and obtained permission from NIH to use up to $3,600 from my research grant for the proposed work with Dr. Luscher. I am therefore proceeding with my plans as related earlier. I also contacted Dr. Stead, to ask if funds of the sort you proposed were permitted by the department. He was entirely agreeable and felt that such uncommitted funds offered greater latitude in opportunity to work and visit in other laboratories, as well as provide enjoyable contact with the commercial firm. From my own point or view the added advantage of being able to conserve my NIH funds in greater part for the operations in my own laboratory which would continue on a limited scale in my absence. Therefore I am free to accept any reserach funds from Merck, if you still feel as before that the type of informal report sent to you last June on our experiences with Indocin constitutes a valid basis for such funds. This type of informal report on our experience can continue to be furnished, although as I recounted earlier, formal reports from here will never be proper due to the long distances our patients travel, making closer supervision impossible. In answer to your inquiry as to institutional and departmental requirements in addressing funds, the funds from Sandoz three years ago were addressed as follows, and this would be the preferred method now:

Name of Payee: Anna H. Hanes Research Fund Dept. of Medicine, payable to Dr. Grace P. Kerby.
Street Address: Duke University School of Medicine.
City: Durham, N. Car., 27706.

Sincerely yours,

GRACE P. KERBY, M.D.

DUKE UNIVERSITY MEDICAL CENTER,
Durham, N.C., December 10, 1963.

DR. NELSON H. REAVEY CANTWELL,
Merck Sharp & Dohme, West Point, Pa.

DEAR DR. CANTWELL: Enclosed are the original data sheets for patients who received Indocin tablets. You will note that some are continuing on capsules. Another 24 patients started on capsules since Aungust 1963, and these data sheets are retained here at present. The presently enclosed sheets represent for the most part those patients covered in the June 1963 summary which I sent to you.

Sincerely yours,

GRACE P. KERBY, M.D.,
Rheumatism Clinic.

NEW BEDFORD, MASS., *February 18, 1964.*

NELSON H. R. CANTWELL, Ph. D., M.D.,
Merck Sharp & Dohme, Research Laboratories,
West Point, Pa.

DEAR NELSON: I am sending to you the initial MK–615 Clinical Evaluations as I originally submitted them. Under comments, where previously no comments had been made on any of the forms, I have brought my data up to date to the time when each patient discontinued the medication.

As you may see from these comments, I failed to note any beneficial effect on either a decrease in steroid dosage or any relief which may have been obtained from these patients who all were suffering from some allergic disorder.

My initial impression after evaluating the original data therefor held it does not seem to be of any benefit in allergic diseases. I might note that I have had four allergic patients with bursitis in whom I took the liberty of trying this drug and had beneficial result in all four. I was patiently waiting the recurrence of my own gout to see if it would be of benefit but fortunately or unfortunately depending upon your point of view, I myself have not had the chance to evaluate it personally.

Because of the poor data I did obtain, I saw no reason to go ahead and use the capsule of MK–615 and have not done so. If you feel there is a dramatic difference in the therapeutic benefit, which I would doubt, I could try a group of selected patients on this if you so desire.

Edward Joyce was in to see me and informed me that you are considering a topical preparation of this which may help in dermatological disorders. I indicated to him that I would be willing to carry out a clinical trial if you felt this was promising.

As far as compensation for the work done, I feel a grant of $1,500 would be fair if you so see fit.

I am sorry you have been too busy to come in to this area. I will be at the American College of Allergy meeting in Miami the first of March. If you have that in your plans I will be happy to see you then. Best regards from Elaine. Hope all is well with you.

Very truly yours,

PAUL CHERVINSKY, M.D.

H. M. MARGOLIS, M.D. & ASSOCIATES,
Pittsburgh, Pa., April 24, 1962.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck, Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: We would appreciate having an additional supply of MK–615.

I am sorry to report, but I am sure you should know, that we saw rather severe dermatitis in one patient after taking four tablets (100 mg) of MK–615 over a twenty-four hour period. The maculosa purpuric rash continued for forty-eight hours. The drug, of course, was discontinued and the dermatitis subsided.

We sincerely hope we will have better results to report in the future.

Sincerely yours,

H. M. MARGOLIS, M.D.

McBRIDE CLINIC, INC.,
Oklahoma City, January 3, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck, Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: Thank you very much for your most recent summary of MK 615. We have used the drug to the extent of our present supply and hope to get our preliminary case reports to you in the near future. In the meantime our supply of the drug is exhausted and we would very much appreciate further supplies of the 50 mg. and 100 mg. formulations.

Certainly this drug is effective in the greater percentage of severe rheumatoid patients and while our experience with the side effects are somewhat more frequent than is your total experience, none of these side effects have appeared alarming in our experience. We have encountered no serious toxicity insofar as laboratory data that we have collected despite the fact that many of our patients have been quite ill. We are particularly impressed with the drug in withdrawing patients from glucocorticoid dependency. Our initial data do not show any clear anti-inflammatory effect of the agent insofar as sedimentation rate or serum glycoprotein concentrations. However, this impression is extremely preliminary.

We have wondered if you are interested in setting up a formal study on the drug and if so what special data are you interested in obtaining? In any event we are most interested in continuing our investigation of the agent and will appreciate further supplies.

Sincerely,

R. W. PAYNE, M.D.

STATE UNIVERSITY OF IOWA,
Iowa City, Iowa, March 13, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: The enclosed is self-explanatory. If you have any suggestions or if anyone has reported such a side-effect, I would be interested in knowing about it. At the present time, I see no reason for going off half-cocked and claiming this is a side-effect.

Sincerely yours,

W. D. PAUL, M.D.

W. C., born June 27, 1910, carpenter by trade, was first seen October 27, 1961. At that time he complained of having pain in both feet, starting in April of 1961. Three months later he had morning stiffness and swelling of the fingers and wrists. Pain was relieved with Anacin. Aside from this, I was able to obtain a history of some shortness of breath on exertion. The physical examination at the time showed fusiform swelling of the fingers and pain in both feet. There was definite evidence of emphysema in spite of the fact that the anterior posterior diameter was not increased and he was a tall, thin individual. ESR was 12 mm/hr. Latex and Bentonite test both were positive. The urine was negative, routine blood counts were normal, x-ray of the chest showed a rather pronounced pulmonary emphysema. He was started on physical therapy, given metatarsal lifts, advised to take Bufferin and Alphadrol.

At that time I felt that the arthritis was more severe than it appeared and that the pulmonary complications preceeded the arthritis, and, was part of the total picture. It was for this reason that he was started on a steroid, Alphadrol being the one we were studying at the time.

We had considerable trouble suppressing this man with Alphadrol and salicylates and saw him many times as he lived near Iowa City. About five months later he began complaining of back pain which at first was not very impressive but after watching him we noticed that he developed atrophy of the left thigh and a loss of the TA reflex on that side. He was seen by the neurologists and the orthopedists and they all agreed that he had a herniated disc at L_5, S_1. Laminectomy was done and herniated discs were removed between L_5 and S_1 and between L_4 and L_5. He made an uneventful recovery. Just before the operation he was switched to prednisone, 1 mg. six times a day.

Following this operation, he developed more involvement of the wrists, fingers, knees, elbows, and ankles. The ESR was 57 mm/hr., and the rest of the laboratory examinations remained the same.

As this man was not being controlled by the steroid, we decided to start him on 50 mgs. of Indomethacin, six times a day. This was started January 30, 1963. The first day or two he had some nausea, but this stopped even though he continued taking the tablets. He appeared to be doing very well and was able to reduce the Buffered Prednisone to 1 mg., four times a day.

About February 16, 1963, he noticed that he was passing coffee-colored urine and that this persisted up to the date of admission on February 26, 1963. At times the urine had the appearance of blood, being dark red. He also developed more dysnea on exertion, cough, and raised a small amount of yellowish sputum. There were no fever or chills, no vomiting, no nausea. There were no urinary symptoms and no edema. He did notice fatigue which has increased during the past week. The physical examination was unusual in that we could find nothing that wasn't present before this episode. Blood pressure was 138/72, both fundi were entirely normal. The joints were less painful, moved better and there was less soft tissue swelling. Liver and spleen were not enlarged. Prostate was essentially normal. A few small areas of ecchymoses were present in the skin which was no different than what he had been having ever since he started taking steroids. The urine was dark red in color, Sp.Gr. 1.023, acid reaction, only a trace of albumin was noted, no sugar. A 4+ chemical reaction for blood was found. The non-centrifuged sediment showed nothing but red cells. Careful examination revealed only an occasional white cell, but no casts. In 1961, the hemoglobin was 15.7 gms., and at this time the hemoglobin was 12 gms. He was sent to the urologist for IVPs. They found a normal urinary bladder and normal retrograde pyelograms. They admitted they could find no cause for the hematuria.

As soon as he was admitted, the Indomethacin was stopped and within two days the urine was clear, Sp.Gr. 1.015, still showing a trace of albumin and six red cells per high powered field after spinning the urine for at least ten minutes. Three days later Indomethacin was started again and by the next morning the urine was again dark red and full of blood cells.

His mother-in-law had died and he was anxious to attend the funeral. Indomethacin was stopped and he left the hospital for the weekend, returning the following Monday. Again the urine was entirely negative except for the very faint trace of albumin. He was started on Indomethacin and after 24 hours had about six to eight RBCs per high powered field (after being centrifuged). The Indomethacin was continued for another day, but did not increase the amount of blood in the urine.

At this point we were totally confused and not sure whether the hematuria was the result of the drug or whether he was developing an acute nephritis with the rare coincidence of having hematuria whenever we started the drug. Not wanting to penalize this individual any longer and increasing his hospital bill, we discontinued the drug, discharged him, keeping him on the salicylates and prednisone and will see him again in two or three weeks. I hesitate to say that the hematuria was directly caused by the drug as we could not reproduce it the third time. I have never seen this happen with salicylates or steroids. Usually these drugs would cause bleeding from the GI tract, but throughout this entire episode the stools were negative for occult blood. I hope to follow through with this man and give him Indomethacin again. I will keep you informed as to what we find out, but at the present, refuse to say that this is the result of the new drug and am keeping this very quiet, you being the only one that we have informed about this episode.

W. D. PAUL, M.D.

DELAWARE AVENUE MEDICAL CENTER,
Buffalo, N.Y., March 20, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme,
Division of Merck & Co., Inc.,
West Point, Pa.

DEAR DR. CANTWELL: Since April of 1962, we have used Indocin on approximately eighty patients. Some of these patients had fairly complete blood profiles; on others, we did less than complete profiles. This group does not represent long-term treatment because some of them absconded, some could not take the drug and some did very well. All of this data we will send to you on separate sheets so that it may be processed and correlated with the data from other sources.

It was my thought that rather than waiting until we had completed the follow-ups on all of these patients, that we should send you a statement for our laboratory costs for the studies done so far. We are breaking this down according to the type of study and the patient involved but the rest of the data will have to follow when we complete each research chart. This statement is enclosed.[1]

To date, the only side effects we have noticed are severe headache and nausea and vomiting. There has been some dizziness in some people and also a slight mental confusion, although this seems to be tied up with the dosage. There are some people who have done well on fairly small amounts; others who have had difficulty on larger doses seemed to be free of symptomatology if we went back to smaller doses and increased very gradually. I also have felt that dosage and salubrious results are not always provable because there is a suggestion that even small doses carried over a long period of time do well. This makes me wonder about cumulative effect.

In summary of this little note, let me say that I believe you have an excellent skeletal analgesic but I am worried about the headache, nausea and emesis and mental confusion.

Sincerely,

HAROLD M. ROBINS, M.D.

UNIVERSITY OF CALIFORNIA MEDICAL CENTER,
Los Angeles, Calif., June 11, 1963.

NELSON H. REAVEY CANTWELL, M.D.,
Research Laboratories, Merck Sharpe & Dohme,
West Point, Pa.

DEAR NELSON: Enclosed is a chart[1] that more or less summarizes some of the information that you asked me about on the telephone the other day. Of the total of approximately 110 patients that we have now treated with Indocin, about 85 of those have rheumatoid arthritis in one form or another. This leaves approximately 25 patients which have had diagnoses other than RA.

Our opinion of the effectiveness of Indocin is changing somewhat within the past few months. Initially, we had many good or excellent results, as can be seen by the chart, but more recently we have had the several features as follows occurring: (1) A few patients that have tolerated the drug for quite some time have become moderately refractory to it now, and are not responding in nearly as satisfactory a fashion as they did early. (2) For some reason or another, we are encountering more side effects from this drug which does not allow us to continue medication in a number of instances. As I told you over the telephone, we have been using doses greater than 200 mg. within the recent past, and this may be in part responsible for some of the side effects. However, in a few of them, we have lowered the dosage to 150 mg. or below, and yet their headache or gastrointestinal symptoms persist in some of these patients, at least. (3) We now have unequivocal evidence of the induction of a peptic ulcer in at least three patients and perhaps in a fourth out of our series of slightly over 100. (4) Two patients, one of which was borderline diabetic to begin with, have shown increased spillage of sugar and an elevated blood sugar while on this medication. (5) Despite all of these features, there are a number of patients who have obtained dramatic results from Indocin and have found it to be as good or better than any other medication that they have been on in the past.

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[1] Retained in committee files.

Some of these patients were not able to work or hardly be ambulant because of the great amount of distress that they experienced. Indocin has allowed them to continue with their activities in a much better fashion than before. (6) Even on very low dosage Indocin to begin with, we have encountered significant numbers of side effects as indicated in the chart. (7) I do not recall how many patients that developed headaches had migraine, but I do know of two people who had a previous history of migraine, each of which developed a very intense headache on a trial of the drug. (8) We have not found Caffergot or other similar medication to have too great a beneficial effect on the headache, and have found the only beneficial thing has been to discontinue this treatment.

In conclusion, Dr. Katz and I feel that this is a very good medication for some people and inappropriate for others. We have not been able to anticipate ahead of time which ones would respond satisfactorily and which ones would not. This medication, or something similar to it, perhaps a chemical variant, seems to have a very definite place in the management of some rheumatic disease cases. However, the incidence of side effects that we have more recently encountered seems to us to be at the present time too great to have this medication used as therapy in general office practice.

Very sincerely yours,

CARL M. PEARSON, M.D.

PORTLAND, OREG., *June 21, 1963.*

DR. NELSON H. REAVEY CANTWELL,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: I am looking forward to seeing you soon. I had a very pleasant talk with Mr. Hilman and Dr. Alpert a few weeks ago. In reply to your questionnaire of the 19th of June, 1963, I am enclosing my answers. As I look over the questionnaire, I can honestly state that I have had no pain relief with the dosage of 150 mg or less. I find that I have to approach a dosage of 200 to 300 mg to get pain relief. However, you must remember that I am only using this drug in the most advanced cases of rheumatoid arthritis—those that have had the disease for a number of years, who are classified as class 3 or 4, who have not responded satisfactorily to any other medication and in many cases are taking the MK615 along with the Tandearil. My incidence of headaches in this group has been about 33%. I have discontinued the drug as soon as headaches occur because I have not known how to evaluate this from a toxic point of view. Until we know more about its causes, I don't think we should continue it in the presence of headaches.

I have had no patients who have developed gastro-intestinal symptoms, ulcers or bleeding.

Sincerely yours,

EDWARD E. ROSENBAUM, M.D.

UNIVERSITY OF CALIFORNIA MEDICAL CENTER,
Los Angeles, Calif., July 9, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme, Inc.,
West Point, Pa.

DEAR NELSON: I wish to take this opportunity to thank you for the very enjoyable evening we spent together in New Jersey during the A.R.A. meetings.

My wife and I have just returned from a pleasant three weeks in Europe, and during that time we had a most profitable, as well as enjoyable, holiday.

In reviewing some of my mail, I see that an Indomethacin questionnaire was sent to me about the time that I left for Europe. I hasten to enclose it to you at this time, and hope that its arrival will not be too late for your series.

I should mention to you that since my return I have learned that two other patients on Indomethacin have developed peptic uclers, one with perforation necessitating operation. This now, in our series of approximately 100 patients, makes at least six, and perhaps seven, ulcers. Certainly this agent is ulcerogenic to a degree that will make it difficult to continue to advise its use. Admittedly, some of the patients are also on small doses of Prednisone, but several of these had been on Prednisone for several years without peptic complications.

One would hope that MK–715, or something similar to it, would not have these deleterious effects.

I wonder if you are going to carry on with your plan of visiting with Dr. Katz and me sometime this summer? We will look forward to such a visit, and hope to hear from you about it soon.

We are preparing our report, and it should be completed within a week. We plan to send it to *Arthritis and Rheumatism*.

Very sincerely yours,

CARL M. PEARSON, M.D.,
Associate Professor of Medicine.

Indomethacin questionnaire

Name of investigator:

1. How many patients have been treated with 150 mg. or less	37
(a) Number who experienced relief of pain	18
(b) Number who experienced relief of swelling and inflammation	5
(c) Number who had definite overall improvement	16
(d) Number unimproved	7
2. How many of the above patients experienced headache	5
3. Of those who had headaches—	
(a) How many had to discontinue the drug because of it	4
(b) How many became tolerant of the headache and continued on the drug	1
(c) How many had relief of their headache at a lower dosage	0
4. How many of the patients experienced gastrointestinal symptoms (abdominal distress, nausea, vomiting, etc.)	4
(a) How many had to discontinue the drug because of these symptoms	3
(b) How many developed a definite ulcer or bleeding	0
5. How many of your treated patients have—	
(a) Chronic rehumatoid arthritis	32
(b) Arthritis or inflammatory disorders other than chronic rheumatoid arthritis	5
6. Does acute inflammatory disease respond better than chronic disease	(1)

(1) Not clearly.

CARL M. PEARSON, M.D.

DELAWARE AVENUE MEDICAL CENTER.
Buffalo, N.Y., July 10, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc.,
West Point, Pa.

DEAR NELSON: Enclosed herewith is the Indomethacin questionnaire which we discussed yesterday on the telephone. The figures represent the combined studies of both the county hospital and the private cases done to date of June 19, 1963, as you requested.

Incidentally, we are in need of more 25 mg. capsules at the hospital so that we may continue uninterrupted on the study. They should be sent to the E. J. Meyer Memorial Hospital, 462 Grider Street, Buffalo 14, New York in care of Dr. C. H. Wilson.

Thank you again for your patience in this matter.

Kindest personal regards.

Sincerely,

HAROLD M. ROBINS, M.D.

Indomethacin questionnaire

Name of investigator:

1. How many patients have been treated with 150 mg. or less	68
(*a*) Number who experienced relief of pain	39
(*b*) Number who experienced relief of swelling and niflammation	15
(*c*) Number who had definite overall improvement	28
(*d*) Number unimproved	32
2. How many of the above patients experienced headache	24
3. Of those who had headaches—	
(*a*) How many had to discontinue the drug because of it	21
(*b*) How many became tolerant of the headache and continued on the drug	5
(*c*) How many had relief of their headache at a lower dosage	6
4. How many of the patients experienced gastrointestinal symptoms (abdominal distress, nausea, vomiting, etc.)	18
(*a*) How many had to discontinue the drug because of these symptoms	8
(*b*) How many developed a definite ulcer or bleeding	1
5. How many of your treated patients have—	
(*a*) Chronic rheumatoid arthritis	25
(*b*) Arthritis or inflammatory disorders other than chronic rheumatoid arthritis	43
6. Does acute inflammatory disease respond better than chronic disease	Yes

HAROLD M. ROBINS, M.D.

THE COLUMBUS MEDICAL CENTER,
Columbus, Ohio, August 19, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., West Point, Pa.

DEAR NELSON: As I indicated to you previously, I have not been impressed with any indication of impairment of kidney function as a result of Indomethacin. The enclosed Scattergram, roughly drawn, gives some indication of the correctness of this position. There is a slight suggestive rise in the BUN after the first few months of therapy but this is more apparent than real because it reflects our interest and concern in a few patients (as indicated by the connecting lines) so that there was a disproportionate number of BUN's done on these few.

I have the bottles containing solution of MK–715 and will immediately put this to use. From previous experience, I am most interested in substituting it in those patients who complained most bitterly of cerebral toxicity from Indomethacin. I think it would be well for you to send me the latest pre-clinical summary on 715.

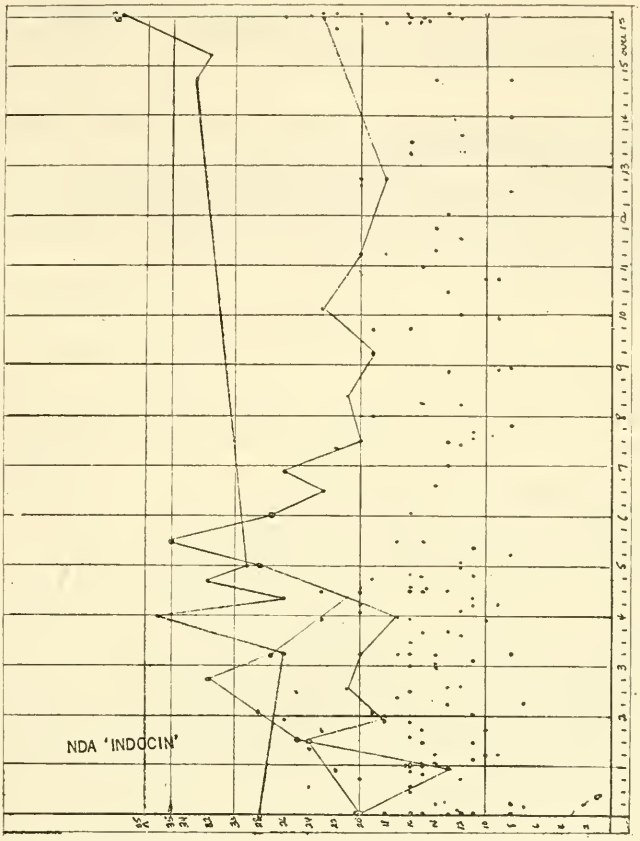
We encountered some delays in doing the blood levels on Indomethacin but are now just about set up to go. If you could run out in the next couple of weeks, I am sure it would be most helpful. I have also been a little delayed in getting patients into the Metabolic Research Unit at the hospital for further studies on daily excretions, as well as more intensive study of blood levels, etc.

How close is Indomethacin related chemically to 715? Is our present method of plasma level determinations basically applicable to 715? Once again, it would seem that the determination of blood levels is all-important to the evaluation of therapy.

Best regards.

Sincerely yours,

NORMAN O. ROTHERMICH, M.D.



Cleveland Metropolitan General Hospital,
Cleveland, Ohio, September 4, 1963.

Nelson H. Reavey Cantwell, M.D.,
Merck Sharp & Dohme Research Laboratories, West Point, Pa.

Dear Dr. Cantwell: Due to Dr. Rammelkamp's illness, which has kept him away from the office for a few weeks, I shall be sending you the report on our experiences in Chile with indomethacin. I am having some figures made up at the moment and it should take another week or two until it is in your hands. I will send along a description of the study and the results so far. In brief, the acute phase data indicate that indomethacin is approximately as effective as aspirin in the control of fever, joints and other acute manifestations. I have been in contact with the people in Chile and it is planned this fall or early winter to perform the final examinations of the patients from the standpoint of heart disease. I shall send the full report in a week or two when the figures arrive.

Very sincerely yours,

Edward A. Mortimer, Jr., M.D.

RENGER CLINIC,
Hallettsville, Tex., September 13, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme,
West Point, Pa.

DEAR DR. CANTWELL: I am getting along very well with Indocin and noticing quite a number of favorable reports.

I have found that it is of little value in rheumatoid arthritis, but in the treatment of the osteo type of arthritis, we are getting very good results.

Could you possibly send me about twenty-five or thirty more bottles of 50 mg. Indocin so that I can carry on the patients that I have using it now for a further length of time.

Sincerely yours,

HARVEY RENGER, M.D.

QUAKERTOWN, PA., *September 19, 1963.*

NELSON H. REAVEY CANTWELL, M.D.,
Furlong, Pa.

DEAR NELSON: I have just completed an intensive review of 85 cases that were treated in our practice with Indomethacin. The range of diagnoses was as follows: traumatic musculoskeletal problems such as low back strain, muscle spasm, fibrositis and the like; osteoarthritis; spondylitis; inflammatory bursitis in acute and chronic form; tenosynovitis; and joint sprains. We have also treated acute febrile illnesses such as thrombophlebitis as well as rheumatoid arthritis.

To suppress inflammatory reaction we found our best results in the 300 to 400 mg. range for daily dosage. We had 10% headache and 5% gastric upset which necessitated stopping the drug and starting at a lower dose level. One woman claimed that her breasts tingled while on the drug; I have not as yet switched her to a placebo to see if this is a true side reaction. In the acute cases pain, soreness and tenderness disappeared quite quickly and temperature returned to normal in all cases, including acute thrombophlebitis, within 48 hours of the onset of treatment. It was interesting to note that the more chronic cases took longer to show improvement but that when the patient was encouraged to continue with the drug, reasonable results began to appear somewhere between 14 and 21 days of treatment.

We had singularly disappointing results in the treatment of rheumatoid arthritis of a long standing nature where the patient had been on steroids for some time prior to the use of Indomethacin. You will, however, be gratified to know that the steroid preparation that has produced the best results in my practice is Decagesic. I could not produce the same results that Dr. W. D. Paul wrote of in March, 1963, when he was able to reduce steroids in rheumatoid cases by the use of Indomethacin addition to the treatment regime. I recall one case in particular of a very marked osteoarthritis of the knees in an obese 60-year-old white woman. Under treatment with Indomethacin with a dose of 300 mg. per day I was able to get this woman to walk normally again and effected over a period of three months a 1¼″ reduction in the circumference of each knee. This was one of the most gratifying results that we saw.

In summary I would state that I believe Indomethacin is an excellent preparation, between Butazolidin and the cortisone derivatives, and I would place it scale-wise two steps above Butazolidin and one step below steroids. I personally feel that it is two to three times as effective as Butazolidin, milligram for milligram, and would definitely prefer to use this in my practice.

I hope this information will help you in your continuing research on Indomethacin.

Very sincerely yours,

FRED J. PHILLIPS, M.D.

MCBRIDE CLINIC, INC.,
Oklahoma City, October 1, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: Perhaps Dr. Robert has told you that we plan to assemble our data on MK 615 for our Arthritis Study Group sometime in November. If you would like we will give you the exact date and it would be a real pleasure to have you attend the meeting. As Dr. Rebert has told you we have developed a rather wide experience with the preparation both in the tablet and capsule form and are really unable to tell any great difference between these two dosage forms. The response to the agent is so variable both insofar as the dose response and patient response that it is going to be very difficult to assign a clear dose response scale for the agent.

At the present time we feel that patients should be started on 50 mg. twice a day and kept on this dosage if tolerable. Otherwise they are reduced to 50 mg. once a day at which point most of them show at least some therapeutic benefit, particularly in combination with Phenylbutazone.

As we also discussed with Dick Rebert we definitely feel that you should set up a double blind on the drug for subjective response, probably at the dosage of 50 mg. twice a day and identical lactose placebo taken one capsule twice a day.

This agent remains one of the most fascinating agents to come along and we continue to feel that it shows great promise in the treatment of rheumatic diseases. However it is with some disappointment that we are reaching the conclusion that the effect of the drug is largely subjective and would most clearly be assigned to the category of analgesics rather than antiphlogistic agents according to our present experience.

Incidentally our supplies of the capsule form of the drug are virtually depleted and naturally we would like as much of both the 25 and 50 mg. capsules as you can readily spare.

Best regards,

Sincerely,

R. W. PAYNE, M.D.

STATE UNIVERSITY OF IOWA,
Iowa City, Iowa, October 3, 1963.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck, Sharp & Dohme Research Laboratories,
West Point, Pa.

DEAR DR. CANTWELL: In reply to your letter of September 25, 1963, I find that we have 91 patients taking Indocin at the present time. Most of these were started on the tablets and capsules of the original MK–615 and a few were started on MK–715. After receiving your letter in August, Dr. Strottmann switched everyone to the new capsules of Indocin. We are still limiting ourselves to treating rheumatoid arthritis, psoriatic arthritis, Reiter's disease and gout. At least ninety per-cent of the patients have rheumatoid arthritis. Recently, we have had about two patients with bursitis who were started on Indocin at the request of the orthopedists. The average dose varies from 150 to 200 mg., a few of the patients requiring 300 mg. per day. At present, we start with 25 mg. twice a day and increase the dose slowly.

The results are much the same as we reported shortly after starting to use MK–615. In a majority of the patients we obtained good anti-inflammatory effects. In a few, excellent results and in about ten per-cent of the patients the results must be considered poor because of side-effects. Subjectively, we would have to rate the drug as very good, while objectively, only fair. The reason for this is that our patients, as you know, are severely involved and even Indocin will not restore the damaged joints.

The side-effects occur in about ten percent of the patients and in nearly one-half of this group, the drug had to be discontinued. The side-effects are nausea, headaches and light-headedness. In a few of these people, we can overcome the side-effects by reducing the dose of the drug. One side-effect that bothers us since we cannot explain it is the peculiar mental change that occurred in two people. The only way we can describe this is to call it some form of hallucination. We have had no bleeding, no change in the blood picture, nor other serious side-effects. Two of the patients that had nausea also had marked pain in the region of the gall bladder. X-ray examination revealed a normally functioning gall bladder and a normal G–I tract. It was necessary to discontinue the drug in both of these patients.

I have a senior student who is tabulating the information on all the patients who were given the tablets and this should be ready within a week or two.

After she completes going over the chart, I will send you a bill for the work she has done.

Sincerely yours,

W. D. PAUL, M.D.

SAN JOSE, CALIF., *January 7, 1964.*

NELSON H. REAVE CANTWELL, M.D., Ph. D.,
Merck, Sharp & Dohme, Research Laboratories,
Division of Merck & Co., Inc. West Point, Pa.

DEAR NELSON: This is in answer to your letter of December 13, 1963.

In the fall of 1962, I submitted data on the tablet form of "Indocin" on the government forms. I have no additional data. My results were generally unsatisfactory and so I discontinued use of the drug.

I have used the capsule form on only 3 or 4 patients with rather indifferent results.

If there is any other information that I can provide, please let me hear from you.

Warm personal regards.

As ever,

JOSEPH E. GIANSIRACUSA, M.D.

YALE UNIVERSITY SCHOOL OF MEDICINE,
New Haven, Conn., January 9, 1964.

NELSON H. R. CANTWELL, M.D.,
Research Laboratories, Merck, Sharp & Dohme,
West Point, Pa.

DEAR NELSON: I must apologize again for my laziness in getting these final reports on the tablet form of MK–615 to you.

As I have told you before, I gave the drug only to chronically ill or seriously ill patients including a variety of patients with collagen diseases other than rheumatoid arthritis. In none of these patients did I see anything very dramatic, but as I say these patients were selected because of their chronic and intractable nature. I did use joint aspiration as a criteria in several of the rheumatoids and there was no affect on the synovial exudate.

I don't believe I will continue to use Indomethacin until some other reports are available from people in this country. I did look over the British Medical Journal report, but the results were just not very clear-cut or well controlled.

The only possible use that I think we might make of it sometime would be in the treatment of acute gout depending on the preliminary results of others. We do see quite a number of acute gouty attacks here, and I think a study of Indomethacin compared with Placebo might be something the house officers might like to undertake some time in the future. However, we have no definite plans at this time.

Sincerely,

J. W. HOLLINGSWORTH, M.D.

UNIVERSITY OF CALIFORNIA, LOS ANGELES,
DEPARTMENT OF MEDICINE,
Los Angeles, Calif., February 14, 1964.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck, Sharp and Dohme Research Laboratories,
West Point, Pa.

DEAR NELSON: I have just had visit from Lloyd Hillman and we have talked over matters about getting the information on MK–615 and Indocin to you as soon as possible. Believe me we are working as actively as possible on this matter, and I hope to be able to make the new deadline that you have recently set.

I mentioned one other brief matter to Mr. Hillman and thought that I would tell you about it at this time. We had one patient that was placed on MK–615 (the tablets) in April of 1963. This 50 year old man had mild or moderate rheumatoid arthrisis with a good deal of pain and distress in the joints. He was on this medicine, in a dosage of approximately 250 mg. daily, for about 10 days and then was discontinued and never returned to the medication again. On his last visit to our Clinic, 10 days after starting the medication, he complained of slight visual disturbance in one eye. As I get the story subsequently, and I have not reviewed his record in detail, he was then seen in Opthamology Clinic where a visual field defect was noted in a quadrant of one eye. It was not felt that this was due to any drug ingestion and he was then referred to Neurosurgery for further evaluation. He did not keep his appointment in Neurosurgery, as I am informed, and hence subsequently dropped out of sight.

The Hospital has recently been served with a lawsuit in very vague terms, although I have not seen the actual details. What this gentleman has in mind is not clear to me at this moment, and certainly so far as I do know, only the Hospital and one of our Hospital Residents are mentioned in the initial papers.

I thought you would like to know about this from the general point of view and perhaps as the months go by some of the details will unfold. In our large series of patients, we have never had specific visual symptoms developing on medication, and it seems to me highly probable that this condition was preexisting in this man or incidentally developed. However, the temporal relationship is such that apparently the administration of the medication may have suggested to him some causal relationship. In a trial program such as this, such matters occasionally unavoidably occur and we must meet them as honestly and properly as we can.

If I hear more details later, I will keep you informed but his note is at the moment merely a preliminary comment about matters as I know them at this time.

Incidentally, the patient's name is Mr. Hershell Hinton.

Sincerely yours,

CARL M. PEARSON, M.D.,
Associate Professor of Medicine.

MERCK, SHARP & DOHME,
West Point, Pa., December 7, 1964.

SUMMARY NDA 16-059

INDOCIN (INDOMETHACIN) CAPSULES

This anti-inflammatory agent (with, in addition, analgesic and antipyretic properties) is indicated in the treatment of rheumatoid arthritis and spondylitis, osteoarthritis, gout and acute bursitis, synovitis, tenosynovitis and tendinitis. (It is noted in the package insert that this last group is described in one section as "musculoskeletal disorders." This requires revision inasmuch as this term also usually implies myositis and fibrositis.) Initial dosage is 25 mg. b. or t.i.d. (in chronic conditions) or 25 or 50 mg. t.i.d. in acute conditions, with increments of 25 mg. daily (acute cases) or weekly (chronic cases). Maximum recommended dose is 200 mg./d. Maintenance doses depend upon patient response. Although the labeling does not so state, this drug is to be used only in adults. (A statement to this effect should be inserted in the labeling.)

The data submitted with this NDA consist of:

A. Chemistry

Indomethacin is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. Its precursors, p-chlorobenzoic acid and 5-methoxy-2-methyl-3-indoleacetic acid, are devoid of the important pharmacologic effects of indomethacin. Although the company does not state the reason for synthesis of this compound, we surmise, in view of its structural similarity to serotonin and 5HIAA (although this similarity is not close), that it was searching for a serotonin-antagonist for rheumatic disorders. As will be seen later, however, animal studies failed to reveal antiserotonin activity.

B. Pharmacology

1. Anti-inflammatory effect—Indomethacin showed a dose-related effect on granuloma inhibition in rats when administered orally and locally. Its potency in this regard was roughly 80 times that of phenylbutazone and 5 times that of hydrocortisone given orally and about 100 times that of phenylbutazone when applied locally. Activity of drug was also seen in adrenalectomized rats. Anti-inflammatory activity was demonstrated when drug was given as a single dose rather than in daily doses and the total single dose required was less than the combined daily dose. The effect of a single dose persisted about one week. Beginning therapy after granuloma is established results in depression of further growth but has no effect on reversing the growth that has already occurred. Indomethacin was effective in preventing edema produced by carageenin and mustard but ineffective against serotonin and various other edema-producing compounds. A combination of corticosteroid plus indomethacin caused greater inhibition of granuloma and edema formation that did the corticosteroid alone.

2. Other pharmacologic effects—Indomethacin was shown to have antipyretic and mild analgesic properties too.

In short term studies the drug appeared to have no effect on urinary uric acid, Na and K excretion or on creatinine clearance and urine flow. Various studies for CNS effects, including EEGs, were negative; also essentially negative were studies relating to atropine-like, adrenergic blocking or ganglionic blocking properties. No effect was noted on B.P., heart rate or ECGs. In dogs with chronic gastric fistulae no effect was noted on gastric acid secretion. Indomethacin appeared to have no effect on calcium metabolsim in short-term studies.

3. Physiological disposition.

Plasma level of indomethacin after oral administration are fairly similar in dogs, monkeys and man, but are considerably higher in rats. Absorption is rapid in all species tested. In man, about half of a C^{14}-labeled dose appears in the urine in the first 24 hours and about 20% appears in the stool at this time.

In three human subjects there did not appear to be evidence of accumulation in the plasma after repeated doses.

Studies in one subject revealed little transfer of drug to CSF. In dogs it was noted that urinary excretion of indomethacin was greater in alkaline than in acidic urine. Probenecid inhibited urinary excretion of indomethacin in the dog. In man most of the material found in the urine is in the form of indomethacin glucuronide. Rabbits, rats, guinea pigs and monkeys, in contrast, metabolize the drug by N-deacylation, 5-demethylation or both and some of the drug is also found as free indomethacin.

4. Some possible side effects:

(*a*) Indomethacin caused retention of H_2O in rats; this was antagonized by the administration of hydrochlorothiazide. In rats the drug was shown to cause gastric mucosal erosions following a single large dose. Indomethacin essentially had no adverse effect on resistance to various bacterial infections in mice and rats and, in some cases, appeared to show a dose-related protective effect. (However, large doses were required for this.) High doses in rabbits decreased resistance to pneumococcal infections.

C. Toxicity studies

1. Acute toxity—Acute oral LD_{50} is 12 mg./kg. in rats, 50 mg/kg in mice, 543 mg./kg. in guinea pigs, 130 mg./kg. in adult rabbits, 135 mg./kg. in neonatal rabbits and above 120 mg./kg in dogs. The acute I.V., s-c, and I.P. LD_{50} in mice and rats are fairly similar to those noted orally for these species, but in the guinea pig, the I.P. LD_{50} is 40 mg./kg.

2. One week oral study in rats given 0, 5, 10, 25 or 50 mg./kg./d. revealed almost 100% mortality in the 3 upper dose levels. None of the lowest dose level or the controls died. Depressed weight gain was noted at the lowest dose level and weight loss at the 3 highest levels. Gross pathologic examination in the rats that died revealed peritonitis in most of them. No drug-related gross path. was noted in the 5 mg/kg group.

3. Thirty-five week oral study was done in rats given 0 or 0.5 mg/kg/d. In two other groups doses of 1.6 or 5.0 mg/kg/d produced physical signs of drug toxicity (weakness, flaccidity, abdominal distention, diarrhea, melena, pollakiuria, chromodacryorrhea and chromorhinorrhea) and because of this, and weight loss and death occurring in these groups, the 1.6 and 5.0 mg. dose level studies were terminated at 4 weeks. The growth rate in the 0.5 mg. rats was unimpaired. Death rate was slightly higher in the 0.5 mg group than in the controls. Hemograms in 0.5 mg group were essentially unremarkable throughout the study except for one WBC differential where there may possibly have been an accidental transposition of the percentages of polys and lymphs.

At the 1.6 and 5.0 mg./kg. dosages anemia and leukocytosis were observed at 4 weeks in some rats. At the end of 4 weeks, gross pathologic observations were made in some rats at all three dose levels and controls. In the 0.5 mg. group no drug-related gross path. was noted. At the two highest dose levels mesenetric nodules and peritonitis were noted and increases in splenic and hepatic weights. Microscopic examination of small intestine at the lowest dose level revealed nothing remarkable. No other microscopic examinations were done in these animals.

4. Thirty-four week oral toxicity study in rats given 0, 0.1, 0.25, or 0.75 mg/kg revealed no effect of the drug on growth rate, mortality, hemograms, weights of heart, liver, spleen, testes; and on gross pathology, except for peritonitis in 2 rats at the highest level; microscopic examination of several control and highest dose rats (liver, kidney, adrenal only) and of all brains from surviving rats of these 2 groups were neg. for drug-related path.

5. Fifty-two week oral toxicity study in rats given 0, 0.5, 1, 2.5, or 5.0 mg/kg/d. in their food revealed high mortality at the highest dose level, only one death

at the next highest level and none in the lower levels and controls. Dose-related physical signs of toxicity were noted in the two highest dose levels. There was a slight effect on weight gain in the highest dose males at the 33rd week. (The highest dose level animals were sacrificed at 34 and 36 weeks). Anemia and leukocytosis with neutrophilia were noted at the highest dose level. Hemograms were essentially unremarkable at the other levels except for a transplant leukopenia in one rat at the 2.5 mg level and a mild anemia at 52 weeks in one rat at the 1 mg level. Organ weights revealed increased liver and spleen weights at the highest dose level in both sexes and increased kidney and testes weights in the males. Gross findings related to drug were confined to the two highest dose levels and consisted of nodules chiefly along the mesenteric attachment of the jejunum or ileum, cystic mesentericnodes, peritonitis, occasional hepatomegaly and splenomegaly. Histopathology (done in controls and two highest dose levels) revealed increased severity of cellular infiltration of the liver and kidney and myelosis of the spleen in the highest dose group. In addition this group showed small intestine ulceration, cystic formation of the mesenteric lymph nodes, marked bone marrow hyperplasia. Two of 19 rats at the second highest dose level showed small intestinal ulceration and one of these also had colonic ulceration.

Administration to rats of the indomethacin metabolites found in rat urine yielded no evidence of toxicity.

A poorly designed study to determine whether rats developed tolerance to the drug revealed no evidence of tolerance for the conditions of the study.

6. Eighteen month oral toxicity study in rats given 0.5, 1 or 2 mg/kg/d. Reports not yet available.

7. Seven week oral study in 16 dogs given 0, 2, 5, 10 or 20 mg/kg/d. produced dose-related vomiting, diarrhea and melena; weight loss and decreased food intake at the two highest dose levels. One animal at the 2 mg level lost weight. H_2O intake and urinary output were non-contributory. Three animals from the two highest dose levels died before termination of the study. Hemograms revealed dose-related anemia at the 3 highest dose levels and in one animal at the 2 mg level. Leukocytosis, and neutrophilia occurred at the three highest dose levels. One animal at the 2 mg level, and one at the 10 mg level showed a decrease in T.P. (mainly globulin) and 1 at the 5 mg level had a decrease in albumin. Uranalyses (no microscopics done), blood glucose, BUN, alk. PO_4, P.T. O.K. One 20 mg dog had a rise in BSP retention. Organ weights (the top dose level dogs had no organ weights determined) revealed thymus atrophy at the 10 mg level and mild splenomegaly at the 5 mg level. Gross findings consisted of gastric and small intestinal ulceration at all dose levels with peritonitis at the 2 upper dose levels. Other gross path. was unrelated to drug. Microscopic findings, besides G.I. ulceration and peritonitis, consisted of liver cell atrophy and inflammation at the 2 highest dose levels, thymic atrophy and atrophy or hyalinization of splenic lymphoid follicles and lymph node follicles in these two groups. Other findings were unrelated. Microscopic examination of the eyes revealed no drug-related path.

8. Fifty-seven week oral study in 8 dogs given 0 or 1 mg/kg t.i.d. (and a concomitant study in 4 dogs given 2 mg/kg. t.i.d. for 6 weeks) revealed weight loss or failure to gain and decrease in food consumption at the 6 mg/d. level. Water intake and urinary output were unaffected. The physical findings noted in the previous seven week study were seen in the 6 mg/d. group. No deaths occurred during the study. Lead II ECGs were said to be unremarkable. Hemograms revealed anemia and leukocytosis at the 6 mg level. Alk PO_4, P.T., SGOT (done at 57 weeks only), FBS, BUN, serum Na, K, Cl O.K. (Electrolyte values were not tabulated but were stated to be within normal limits.) Hypoproteinemia occurred at the top dose level. One dog at the 3 mg level had transient rise in ESR and one 6 mg dog had slight increase in BSP retention. Albuminuria occurred at the highest level and transiently at the 3 mg level. Hematuria (occult) occurred at the 6 mg level. Microscopic examination of urine was not reported. Organ weights revealed increased adrenal weight in one dog at each dose level, increased spleen weights in two dogs at the 3 mg level and decreased spleen weight in one dog at the 6 mg level. Pertinent gross findings were limited to the high dose group and consisted of G.I. ulcerations and peritonitis and, in one dog, thymus atrophy. (The latter was not reflected by organ weight/body weight ratio.) Histopathology studies were limited to the 3 mg dogs. One treated dog had thyroiditis. The possible significance of this to drug ingestion is not

known. Other microscopic findings could not be considered drug-related. Examination of the eyes revealed retinitis in one treated dog.

9. 129 week study in 16 dogs given 0, 0.25, 0.5 or 1 mg/kg/d. (and a concomitant study on 4 dogs given 0.5 mg/kg/d. for 28 weeks) revealed no deaths, rare vomiting, diarrhea and overt melena. Fecal occult blood was frequent in the highest dose groups. Lead II ECGs were said to be unremarkable. Reports of fundoscopic examination by an M.D. were stated as revealing arteriolar sclerosis in a large number of treated dogs, none in the controls. However, in view of the surprising nature of this finding, a D.V.M. examined the dogs and found minor, insignificant arteriolar changes in two control and two treated dogs. (See also memo of telephone conversation dated 10/23/64.) There was also unilateral focal retinal vasculitis in two treated dogs which healed or were healing spontaneously and were felt to be non-drug-related. Two treated dogs had unilateral cataracts, felt to be congenital. All dogs gained weight. Food intake appeared to be somewhat depressed in some of the highest and next highest dose dogs toward the end of the study. Water intake and urine output were unaffected. Hemograms (including retics., platelets, clotting time), FBS, BUN, urinalyses, P.T., SGOT (terminal study only), alk, PO_4ase, BSP, glucose tolerance, serum electrolytes (terminal study only), serum proteins, were unaffected except for rare, transient, non-drug-related abnormalities and eosinophilia in some dogs, probably due to parasitism. Reports of microscopic urinalyses were not included but a statement was made that no drug-related path, was noted. The urines were stated to be neg. for occult blood.

Organ weights revealed thymus atrophy at the two highest dose levels, decreased spleen weight in one high dose dog, depressed drenal weights at the two highest dose levels and prostatic enlargement in one high dose dog. Pertinent gross lesions consisted of small intestine ulceration in the two highest dose levels. Pertinent microscopic findings consisted of focal shortening and disappearance of intestinal villi and focal thinning and thickening of the submucosa in the two highest dose levels. An increased incidence and degree of severity of lymphocytic thyroiditis was noted in the treated dogs. The possible relationship to drug is not known. Microscopic examination of the eyes revealed no drug-related pathology.

10. Four week study in 8 dogs given 0 or 5 mg/kg/d. I.V. revealed weight loss in one control and one treated dog, and decreased food consumption in these dogs. Diarrhea and melena occurred in the treated dogs. Water intake was unaffected but urinary output was decreased in some of the treated animals. The treated dogs developed anemia, leukocytosis, neutrophilia in some cases and a shift to the left; also albuminuria and hypoproteinemia (chiefly hyphoglobulinemia). Elevated ESR, BUN, alk, PO_4 were seen in three dogs (1 abnorma./dog). prostatic hypertrophy in one control dog. Pertinent gross lesions were limited to the usual G.I. ulcerations and peritonitis. Histopathology revealed inflammatory reactions in liver, pancreas, kidney, and liver cell atrophy. Sections through the injection sites yielded no changes which could be directly related to indomethacin. The G.I. tract was not examined microscopically.

11. Rectal administration in dogs of 105 mg indomethacin suppositories (approx. 8 to 12 mg/kg) q.d.×4 resulted in emesis and diarrhea. Determinations of plasma levels of drug revealed rapid absorption, as a rule, with, usually, low plasma levels after 24 hours. At autopsy (on day 5) ulcerations were found in the stomach and small intestine.

12. Six week study in 8 monkeys given 0.2 or 5 mg/kg/d. revealed diarrhea, melena, weight loss and anorexia at both dose levels; anemia and, in one animal, transient leukocytosis, were noted. One animal from each dose level had a rise in BUN. Alk. PO_4ase was unchanged. There were no other lab tests done. Two animals died shorlty before termination of the study. Cause of death was not determined. Organ weights revealed thymic atrophy at both dose levels. Gross examination revealed no drug-related path. Microscopic examinations (done at the 5 mg level only) revealed no drug-related path.

13. Eight week study in 24 monkeys given 0; 1 mg/kg increasing to 2 mg/kg; 5; or 10 mg/kg/d. revealed anorexia, vomiting, diarrhea and melena at the 5 and 10 mg levels. Three animals at the 10 mg level were sacrificed during the 2nd week because of poor physical condition. Weight loss occurred at the highest level and in one animal each at the 5 mg level and the 1-2 mg level. Hemograms revealed development of anemia in a few monkeys (noted at each dose level), occasional leukocytosis and elevated ESR. BSPs were intermittently elevated in both control and treated animals. Alk. PO_4ase, SGOT, serum bilirubin O.K.

BUNs were intermittently elevated in control and treated animals. No other lab studies were done. Organ weights revealed thymic atrophy in some animals (mostly female) at all dose levels and increase in thyroid weight in one high dose female. Gross examination revealed no findings which could be definitely attributed to drug except possibly for small hyperemic areas in the mucosa of the stomach and ileum in the two highest dose levels. Microscopic examination was limited to the eyes. No pertinent pathology was noted.

14. Eighteen week study in 24 monkeys given 0, 1, 5 or 10 mg/k/gd. revealed one death in a control monkey, and three deaths in the highest dose group. In addition, one animal in the low dose group was sacrificed at 16 weeks because of poor physical condition and one animal at 5 mg died. All dose levels displayed anorexia, vomiting, diarrhea and melena. Patchy alopecia noted in two monkeys in the middle dose group was felt to be non-drug-related, since this has been noted previously in controls. Weight loss was confined to the highest dose level. Hemograms revealed a severe anemia in one high dose monkey with mild anemias in others at all dose levels, usually with recovery from the anemia by the end of the study. Some treated animals and two control monkeys developed leukocytosis with a relative lymphopenia and neutrophilia and, in a few cases where leukocytosis did not occur, a relative neutrophilia was noted. Except for the animal with the severe anemia, serum electrolytes were O.K. (except for transient borderline decreases). In the animal with anemia, serum Na and C1 dropped and K rose. This animal also had a marked rise in BUN. Other treated animals had some BUN elevation, usually intermittent. Elevations of BSP (usually intermittent) were seen in control and treated animals. P.T., clotting times, serum cholesterol appeared unaffected. Transient SGOT elevations were seen in control and treated animals. No other lab studies were done. Organ weights revealed thymic atrophy in some treated animals, particularly female, increased adrenal weight in one middle dose male, and decreased pancreatic weight in some animals at all dose levels. Gross examination revealed no findings which could be definitely attributed to the drug except perhaps for focal mucosal hyperemia of stomach and colon (in the latter location it was also noted in one control monkey) at all dose levels (not seen in all animals) and, in one monkey at the 10 mg level, focal thinning of the wall of the colon. Pertinent microscopic findings consisted of moderate fatty infiltration in the liver of two high dose animals, ulcer in the gall bladder of one monkey at 10 mg, moderate to marked loss to zymogen granules in the pancreas at all treatment levels (felt to be related to debilitation), atrophy and macrophages in mesenteric lymph nodes, gastric ulceration in one high dose monkey, colonic ulceration at all dose levels and in one control animal, mucosal thinning of the colon in one high dose animal, increased M/E ratio in the marrow of one low and one middle dose animal and left shift in the marrow of the latter animal and one high dose animal. Other findings were non-drug-related or secondary to debilitation. Examination of the eyes revealed no drug-related pathology.

15. Nine to twenty-two week study in 40 rabbits given 0, 1, 5, 10 or 20 mg/kg/d. Mortality was high at all dose levels but occurred earlier in the 20 mg group. The surviving animals of the 10 and 20 mg group were sacrificed at the end of nine weeks. The one and five mg survivors were kept on drug for almost 22 weeks. Some of the controls were sacrificed at 9 weeks and some at 22 weeks. Occasional diarrhea, weakness and anorexia were noted in the treated animals. Fundoscopy was stated to be negative throughout the study. All animals that survived to sacrifice maintained or gained weight. Hemograms were essentially unremarkable. ESR was elevated in 2 animals before death and in one animal transiently.

Organ weights revealed spenomegaly in one high dose female and enlarged pancreas in one female at the 5 mg level. Thumus atrophy occurred in controls and treated animals. Gross examination revealed gastric ulceration in the 20 mg group and increased evidence of infection (subcutaneous and pumonary abscesses, pneumonia and pericarditis) among the treated animals. Pertinent microscopic findings (only the 5 and 20 mg. levels and the controls were examined), in addition to the lesions described above, consisted of decrease in size of splenic lymphoid follicles, salivary gland inflammation at the highest level (usually extension from subcutaneous abscess), marked thymic atrophy at the highest dose level. Other changes were related to the primary infectious processes.

16. Five week study in 50 guinea pigs given 0, 10, 20, 100 or 200 mg./kg. I.P. This study was not very detailed and will not be discussed.

17. Additional studies were done in guinea pigs, cats, pigs, mice and chickens. With the exception of the last animal, G.I. ulcerations occurred.

18. Reproductive studies:

Placental transfer of labeled indomethacin was demonstrated in the fetuses of pregnant mice. The concentration of radioactivity in the fetuses ranged from 7 to 22% of that found in maternal carcasses.

A 2-generation reproductive study in mice fed 0, 0.1, 0.5 or 2.5 mg. indomethacin per kg. diet was essentially unremarkable. During the second generation study it was estimated that the daily intake of drug was about 0, 0.02, 0.1 or 0.5 mg./kg.

A 2-cycle reproduction study in rats fed 0.5 to 0.66 mg./kg./d. revealed increased litter mortality during the first four days in the animals from treated mothers who cast naturally. This was noted in both cycles. There was also an increased number of pups who were cast dead in the treated group in both cycles. No fetal abnormalities were noted.

In a study in pregnant rabbits given 0 to 2.5 mg./kg./d. during days 8 through 16 of gestation there appeared to be no adverse drug effects on fetal viability, etc. One treated dam failed to survive to term.

19. An I. M. irritancy test in rabbits given 0.5 ml. of a 1% soln. (5 mg. in 0.5 ml.) revealed that this drug is much too irritating to be given by this route.

D. Clinical pharmacology

1. Normal adult volunteers (76) were given 75 mg./d. increasing to 150 mg. b.i.d. over a 24 week period. Another 24 volunteers received placebo. Wt., P.R., B.P., FBS, BUN, SGOT, serum chol., T.T., serum bilirubin, alk. PO_4ase, urinalysis (no microscopic), hemograms (including platelets) and stool guiac were determined periodically. Wt., P. R., B.P. were unaffected by drug. T.T. and alk. PO_4ase occasionally showed transient elevations in drug-treated subjects, however, T.T. also fluctuated in the placebo group. Two treated subjects developed a mild anemia (1 of these had a 1+ stool guiac on 1 occasion), however, 2 placebo volunteers also showed mild anemia. Two treated subjects developed a peptic ulcer and 1 of these also had a tarry stool (no anemia when Hgb determined, which was several weeks after bleeding episode).

Some treated subjects had transient trace to 2+ stool guiaces. Occasional positive stools were noted in the control group.

One subject had a rise in SGOT, serum bilirubin and T.T. noted at the end of the study. These abnorm. disappeared rapidly and did not recur on challenge with the drug. The outstanding side effect was headache, reported by over half of the treated group (no headache in placebo group). This usually occurred early in the study and lasted for 1 to several days. In the few cases in which a description was obtained, it was characterized as occurring early in the day and accompanied by feeling of pressure. Three subjects stopped drug between 4 to 8 weeks because of headache, dizziness, lightheadness, nausea. These symptoms were also commonly noted in the other treated volunteers. Urticaria or rash was seen in 3 treated subjects with spontaneous clearing during continued drug administration or lack of recurrence following reinstitution of drug. Another 2 had rash felt not due to drug.

2. Absorption, excretion and metabolism—in 3 patients with R.A. given a single dose of labeled indomethacin, 56 to 80% was recovered in the urine over a 5 day period. The highest rate of excretion occurred during the 1st 4 hours and over ¾ of the total excreted dose appeared during the first 24 hours. Peak plasma conc. were observed at 1 hour and by 24 hours there was little radioactivity in the plasma. The plasma half life was estimated as 87 min.

Absorption studies with tablets and capsules in healthy volunteers revealed marked variability (based on plasma levels of drug) in the same individual on different days but, in general, absorption of the capsules appeared more promptly and produced higher initial blood levels, though by 4 hours there was little difference. In one human subject about 15% of an administered dose was recovered in the bile, however, plasma levels of drug were low in this individual so that amt. absorbed is not known. In 8 normal adults no effect of drug on urinary 17–OHCS excretion was noted and in 3 no effect on urinary creatinine and 17–KS and plasma 17–OHCS was observed. In 8 normal subjects given 200 mg/d. x 10 d. no effect was noted on clotting time, bleeding time, tourniquet test, clot retraction, fibrinolysis, P.T., serum prothrombin, partial thromboplastin and platelet counts.

3. Fecal blood loss—In Cr^{51} tagged RBC studies in 5 normals given ASA 2.4 Gm./d. x 7 d. or indomethacin 200 mg./d. x 7 d. mean fecal blood loss/d. during control periods was 0.7 ml.; during ASA 2.2 ml./d.; during indomethacin 1.7 ml./d. In another study in 28 normals the levels were 0.6, 1.95, (indomethacin)

and 4.58 (ASA). The range for indomethacin was 0.3 to 6.0 ml./day and for ASA 0.2 to 32.8 ml./d.

4. Mechanism of indomethacin-induced headache-Sicuteri in an uncontrolled study felt that the mechanism is a vasoconstrictor effect on the cephalic vessels with a subsequent vasodilator rebound resulting in headache.

E. Case reports—Tablets

1. Atkinson—Uncontrolled study in 4 adults with R.A. (including 3 with psoriasis) treated with 150 to 200 mg./d. for 2 weeks to 8 months. Good results in 2 patients. No adverse effects on a multiplicity of lab. tests except for occasional positive stool guiacs. The drug did not lower elevated ESR. Skin rash developed in 2 and dizziness in 1. One patient with a history of gastric ulcer on steroid therapy had no G.I. symptoms during 6 months of indomethacin.

2. Bilka—Partially controlled study in approximately 135 adults (126 with R.A., no cases of diagnosed bursitis although the company's summary states there was 1 case, and 9 with miscellaneous disorders) (some case histories were duplicated) given usually 50 to 200 mg./d. (in divided doses b. to q.i.d.) for 1 to 8 weeks in most cases. A few cases were treated for 11 months or more. Most patients received ASA, steroids or gold concomitantly. Response was good in 39, fair in 39. Reduction or discontinuation of steroid dosage was accomplished in 12 of 51 pts. receiving concomitant steroids. The reductions were not spectacular in amount. The study was partially controlled in that single-blind studies were done in a few patients substituting placebo for 2 weeks somewhere during the treatment period. There is no mention in some cases concerning when the placebo was given. Since remission of symptoms has persisted for several weeks after indomethacin has been withdrawn (this has been demonstrated by others) if placebo was substituted after start of drug, a good result with placebo may have been due to drug (or spontaneous remission). In some cases there was exacerbation of symptoms when patient was switched to placebo following drug. In general results were better when daily doses over 100 mg. were used. The most frequent side effects were headache (18 pts.) (which sometimes disappeared when drug was continued, was sometimes relieved by diphenyldramine and sometimes required reduction in dosage or withdrawal of drug) and G.I. distress (20 pts.) including, in 4, activation of an old peptic ulcer or appearance of ulcer with no previous history. One of the 4 developed phlegmenous gastritis, superficial gastric ulceration and pyloric obstruction requiring gastric resection. Dizziness was noted in 7 pts., skin rash in 1, edema in 1. Lab. tests (SGOT, alk. PO_4ase, ceph. floc., BSP, T.T., serum bilirubin, hemograms, urinalyses, serum alb. and glob., BUN, FBS, stool guiacs) revealed scattered changes in some areas but, with the exception of positive stool guiacs, relationship to drug cannot be stated with certainty. Some patients showed positive ceph. flocs. during therapy with no base line determinations done. Some showed transient elevations during therapy.

Some had elevations prior to indomethacin. BSP elevations occurred occasionally with drop to normal when drug was withdrawn. Elevated SGOT seen in 2. Two patients with leukopenia (1 with relative neutropenia also) prior to drug showed no adverse effect from drug. One patient developed a mild leukopenia with relative neutropenia gradually over a period of about a year and during continued follow-up showed a normal count on a few occasions while still on drug. This is probably not a drug effect. Some patients had transient albuminuria and microscopic hematuria. Other lab. tests were unremarkable with respect to possible drug effect.

The low incidence of good response in this group of patients may have been due to the fact that the disease was of long-standing in most of the patients, in addition to the low dosage used in many.

3. Brown—9 patients with R.A. or Reiter's syndrome given 30 mg./d. in a double-blind cross-over (1 week drug, 1 week placebo). Some felt better on placebo. A few noticed striking difference between the 2 with better results on drug.

4. Calabro—Uncontrolled study in 27 adults with R.A. or rehumatoid spondylitis and 1 with psordiatic arthritis given usually 100 to 150 mg./d. in 3 or 4 divided doses for a few weeks to over 1 year. Many were given concomitant ASA or steroids. Good results were seen in 10, fair in 11. One of 5 on steroids was able to reduce steroid dosage. Lab tests revealed many patients with positive stool guiacs, SGOTs and PTs were transiently elevated in some patients. Elevations of these 2 tests were also seen pretreatment in some with return to normal

during therapy. Ceph. flocs. fluctuated. Fluctuation of BUN was seen in 1 patient who also had albuminuria and glycosuria on a number of occasions. This patient was also on hydrochlorothiazide. One patient had rise in BUN to 78 after 9 weeks with no follow up. This patient was dropped from the study after 3½ months (not because of BUN elevation). One patient developed anemia with no overt signs of bleeding; no stool guiacs were done in this patient. Side effects consisted of headache in 11, G.I. distress (N., V., D., "heartburn") in 9, dizziness in 5, bleeding of active gastric ulcer present prior to indomethacin.

5. Chervinsky—Uncontrolled study in 20 adults (19 with asthma, 1 with dermatitis). No comment will be made concerning results since asthma is not one of the claimed indications for this drug.

6. Clark—No case reports but lab. results on 11 patients followed up to 9 months (dosages not stated nor is there comment concerning concomitant therapy). One patient showed a mild leukopenia after 7 months with no follow up. Fluctuating ICD values were seen in a few patients. No stool guiacs were done.

7. David—Uncontrolled study in 22 adults (21 with osteoarthritis, 1 with R.A.) given usually 50 to 100 mg./d. in divided doses for a few weeks to over a year. No concomitant therapy was given except for ASA in a few. Results were good in 19. Side effects consisted of G.I. distress in 4 and headache in 1. Scattered hemograms and urinalyses O.K.

8. DeMartini—Testimonial letter concerning good results in acute gout and rheumatoid spondylitis with "spotty" results in R.A.

9. Duff—1 patient with R.A. given 200 mg./d. along with ASA and prednisone for 6 weeks. Poor result. Patient developed diarrhea and after 4 weeks epistaxis. Platelets were normal. No P.T. or other hematologic tests done.

10. Engleman—Uncontrolled study in 64 adults (including 55 with R.A. or rheumatoid spondylitis, 7 with osteo. of the hip, 1 bursitis) given usually 50 to 200 mg./d. in divided doses for a few weeks to over a year. Most patients received other concomitant anti-arthritic therapy. Of 17 on steroids, only 1 could reduce the steroid dose. The usual side effects occurred. In addition, mental confusion, depression, inability to concentrate, feelings of unreality, blurred vision, phlebitis or edema occurred in 1 to 3 patients (for each symptom). (The patient with phlebitis was also on steroids at the time.) Results were good in 8, fair in 11. The results in 1 patient with pursitis was not reported. Pos. stool guiacs were not as frequent in this group of patients. Other lab. tests revealed no apparent drug effect except for a possible effect on SGOT—3 showed rise with no follow-up. (One patient had transient rise with leukocytosis and "flu-like symptoms" with return to normal while still on drug.)

11. Englund—Several letters stating that he has gotten good results in acute and chronic gout, rheumatoid spondylitis and in active R.A., less response in far-advanced R.A. with little inflammatory disease. Practically all patients were also on steroids and in many, dosage of steroids could be reduced or eliminated entirely. The patients with gout initially took drug regularly but later it only when an acute attack was pending, usually aborted by 1 or 2 doses. Improvement in some of the rheumatoids was not seen until weeks had elapsed. The usual side effects were noted, including headache in over 50%. Most of the headaches were minor and transient and disappeared despite continuation of drug. In addition, diplopia was noted in 2 of 94 patients, scotomata in 1.

12. Giansiracusa—Uncontrolled study in 9 adults (6 with R.A.) treated for up to 8 weeks with 50 to 200 mg./d. Results good in 5, fair in 2. In a later summarized report, however, this investigator stated that with further experience in more R.A. patients he had obtained poor results and discontinued use of the drug.

13. Gordon—12 patients with eye disease. Will not be discussed since this is not an indication.

14. Grossman—2 patients with R.A. given 50 to 200 mg./d. for several months with good results. No concomitant therapy given. No adverse effect on laboratory tests.

15. Holley—3 patients with R.A., 1 of whom obtained good relief of acute symptoms with indomethacin but when concomitant salicylates were withdrawn (had been on salicylates also prior to indomethacin), there was prompt return of symptoms.

16. Hollingsworth—Uncontrolled study in 9 adults (5 with R.A.) given 50 to 300 mg./d. for 5 weeks to over a year. Most received concomitant ASA or steroids. Of the patients with R.A., 2 showed mild response (1 was able to lower steroid dosage).

17. Jessar—Uncontrolled study in 31 adults (30 with R.A. or spondylitis) given usually 50 to 200 mg./d. for a few weeks to over a year. Most were on concomitant therapy. Good results were seeen in 19, fair in 8. Of 14 on steroids, 3 were able to lower dose or discontinue. Besides the usual side effects, skin rash was noted in 2. Besides the positive stool guiacs, laboratory tests were unremarkable relative to drug effect with the possible exception of mild anemia in 2 patients. Whether this was due to the disease or fecal blood loss from the drug cannot be stated.

18. Kanof—Patients with skin disease. No discussion here.

19. Kerby—Uncontrolled study in 22 adults (21 with R.A.) given 50 to 400 mg./d. for a few weeks to almost a year. About half received concurrent ASA and 1 received a steroid. Good results were noted in 13, fair in 2. Side effects consisted mainly of headache. There was no G.I. distress. There was 1 possible severe CNS disturbance; Nystagmus, diplopia and palatal weakness in a patient with acute flare-up of Still's disease. One patient with SLE and nephritic symptoms showed a rise in BUN while on drug with drop to normal after withdrawal. Laboratory tests fairly unremakable except for 1 mild anemia with return to normal after $FeSO_4$ and the usual positive stool guiacs. Transient fluctuations in T.T. and ceph. floc. noted, 1 case of transient mild hyperglycemia and 2 mild hyperglycemia with no follow-up. One with elevated FBS pretreatment had normal levels during therapy.

20. Kling—Uncontrolled study in 26 adults (17 with rheumatoid disease, 8 with osteoarthritis) given 50 to 250 mg./d. for, usually, no more than 4 weeks (in a few up to 9 weeks). Steroids were given concomitantly in 12. Of these, 5 decreased steroid dosage and 1 discontinued it. Good results reported in 13, fair in 4. G.I. disturbances were most common in this group, little headache. A few had laboratory tests with no adverse drug effect noted. No stool guiacs done.

21. Kuzell—Uncontrolled study in 27 adults (including 19 with R.A. or spondylitis, 5 osteo., 4 gout, 1 "fibrositis") given less than 50 mg. to 300 mg./d. for a few weeks to over a year. A number of patients were on concurrent antiarthritic therapy.

One was able to reduce steroid dosage. Results were good in 11. Headache was not prominent but G.I. distress was, requiring discontinuance of therapy in many. Three cases of peptic ulcer occurred but all 3 were also on steroids.

Another patient had multiple ulcerations in stomach, duodenum and jejunum. Toxic psychosis was reported in 1 patient. (This patient was on imipramine for mild depression.) Fluctuations in alk. PO_4ase and ceph. floc. in some pts. probably unrelated to drug. A few pts. had mild elevation of BUN.

22. Lockie—Uncontrolled study in 22 adults (including 14 R.A., 6 osteo.) given less than 50 to 250 mg./d. for a few weeks to over a year. Most received concurrent anti-arthritic therapy. Good results were noted in 13, fair in 5. Of 10 on steroids, 5 decreased dose, 1 discontinued them.

The usual side effects were noted. A number of patients were taken off indomethacin and developed excerbation of symptoms with relief when restarted. A number of pts. with osteo, were said to have pain relief on drug. No adverse effect of drug on lab. tests, although 1 pt. had slight elevation in BUN (possibly due to drug).

23. Norcross—Uncontrolled study in 150 adult pts. (including 92 with R.A., 62 with osteo., and 4 with gout) given less than 50 to over 300 mg./d. for a few weeks to over a yr. About ⅓ were on concomitant antiarthritic therapy. The usual side effects, including 9 cases of peptic ulcer (2 perforations) were noted. Some of the pts. had multiple peptic ulcers. Skin rash, phlebitis, stomatitis occurred in 1 pt. each. Results were good in 114, fair in 13. Of 39 on steroids, 11 discontinued and 4 reduced dosage. A few pts. developed mild to moderate anemia (ulcer in 2 of these, positive stools in others). One pt. developed severe anemia with markedly positive stool guiacs but neg. Ba enema and esophagram. (Presumably G.I. series was also done but this is not stated.) One pt. had marked anemia with no work up. Some pts. showed mild increase in BUN, transient in most. One patient had a simultaneous performation of a peptic ulcer and of a carcinoma of the sigmoid colon. A few patients had marked bleeding from their ulcers. In a paper presented at the ARA meeting in 1963 Norcross stated that many R.A. patients were switched to placebo Tabs. with prompt relapse of symptoms in most. Also many showed relapse on attempts to reduce the daily dosage. This liberal use of placebo Tabs. is not mentioned in the case reports, with rare exceptions.

In this paper he also states that 5 patients with an elevated BUN from drug had creatinine clearance, RPF and renogram determinations. These were also done in 2 normal volunteers given drug. Abnormalities of all 3 parameters were seen in most of the subjects studied. In 1 normal individual retested after withdrawal of drug the findings returned to normal levels. We called Dr. Norcross about this and he now feels that perhaps his judgment of renal function impairment was too hasty, that the changes were borderline, although in 1 subject he still thinks it is definite. He is going to do more studies, but has not started them yet.

24. Paul reported a case of marked hematuria in a patient on indomethacin for 2 weeks. Whether or not it was due to drug cannot be determined from the data presented.

25. Payne—Uncontrolled study in 67 adults, 1 child, with R.A. (62), rheum. spon. (4) and osteo. (1) given 50 to 300 mg./d. for less than a week to 11 months. A few received concomitant phenylbutazone or steroids. Good results were reported in 38, fair in 21. Two of 6 pts. on steroids decreased steroid dosage. The incidence of side effects was high. In addition to the usual there were 15 cases of edema and 3 of skin rash.

Of the pts. with edema only 1 was on concomitant steroids and 1 on phenylbutazone. These reports are of little value with regard to therapeutic eval. of drug. One pt. developed a marked anemia after 6 days with no comment by the investigator and no follow-up (drug was withdrawn). A number of patients developed mild elevations of alk. PO_4ase.

26. Pearson—Paper on his results in 97 mainly R.A. pts. Unlike Norcross, who stated that in his R.A. pts. benefit often was not noted for weeks, Pearson stated that beneficial results were noted in 24 to 48 hours if they occurred at all. (It may be, however, that when he noted no benefit in 1 or 2 weeks he dropped the pts. from the study.) There were 50 discontinued "for one reason or another" (37 for side effects.) A few pts. were in a single blind study of drug and placebo with crossover after the first week. Patients who received drug first and benefited (8) and were then switched to placebo developed severe exacerbations within 24 hours. However, 1 of these, after 4 days, and while still on placebo, returned to his symptom state similar to that noted on indomethacin, so in this pt. at least. exacerbation was not due to drug withdrawal. The usual side effects were noted plus syncope in 1 individual due to "lightheadedness". A diabetic patient was said to have increased hyperglycemia and glycosuria while on drug. One patient had an elevated SGOT (no base line) and 1 developed high alk. PO_4ase.

27. Phillips—Uncontrolled study in 41 adults with R.A. (10), osteo. (16), bursitis (3), gout (2) and miscellaneous musculoskeletal conditions given 50 to 300 mg./d. for a few days to over 6 months. Only 2 were on concurrent antiarthritic drugs (steroid and probenecid). Results were good in 27, fair in 4. The usual side effects were noted including overt bleeding peptic ulcer (2). Lab. tests that were done were unremarkable. The fact that almost all of the pts. had an alk. PO_4ase of exactly 3 B.U. casts doubt on the validity of the results of this test as performed by the involved lab.

28. Plotz—Uncontrolled study in 94 adults with R.A. or rheum.spond. (54), osteo. (52), gout (2) and miscellaneous disorders given 50 to 200 mg./d. for a few days to over 6 months. Concomitant steroids were given in 21 cases. Results were good in 64, fair in 10. Side effects were the usual but they were not as frequent as in some other studies. This may be due to the relatively low doses used by this investigator (frequently no more than 30, 45 or 75 mg./d.)

Lab tests revealed anemia in 1 patient. No stool guiacs done. One pt. developed leukopenia after 18 months (dosage not stated) with return to normal when drug was withdrawn. Platelets were stated to be adequate but the pt. noted a few purpuric spots. Diff. was normal. Drug was not restarted.

Of the 21 on steroids, 13 discontinued and 4 decreased their dose.

29. Rammelkamp—Paper on use in rheum. fever. This is not one of the indications and will not be discussed except to note that the investigator stated that no side effects attributable to indomethacin were observed.

30. Robins—Uncontrolled study in approximately 75 adults with R.A. (42), rheum. spon. (5), osteo. (26), gout (5), bursitis (6), fibrositis (3) and miscellaneous disorders given less than 50 to 300 mg./d. for 1 day to over a year (most less than 2 months.) Concomitant steroids were received by 18 and antimalarials by 4 (no phenylbutazone).

The usual side effects were noted including 1 possible case of peptic ulcer. There was 1 case of stomatitis and 1 of peripheral numbness. Results were good in 41, fair in 9. Steroid dosage was discontinued in 2. Anemia developed in 3 patients (only rare stool guiacs were done on the pts.). A few showed a mild rise in BUN. Results in bursitis were variable.

31. Rothermich—A single blind study in 65 adults with R.A. or rheum. spon. (59), osteo. (5), gout (4) and miscellaneous disorders given less than 50 to more than 300 mg./d. for a few weeks to over a year. Most were receiving concomitant steroids or ASA. Good results were reported in 48, fair in 7. Of 39 on steroids, 16 discontinued or decreased the dosage. With the exception of a bleeding sigmoid diverticulitis and 1 case of perforation of peptic ulcer, G.I. side effects were practically absent. Headache and dizziness were the chief complaints. One patient fell off a ladder because of dizziness. (A precautionary note concerning vehicular and machinery operation should be in the labeling.) Paranoid tendencies and depression were reported in some patients. In a letter from the investigator it is stated that among the patients in his study, 128 relapses were produced by substituting placebo. Although he stated some of his studies were double blind this is not supported by his case reports (single blind only). All patients were first started on drug and shifted (in many cases) to placebo for brief periods after control of symptoms. He also stated that his continued use of the drug has led him to conclude that it is of little value in chronic fibrositis or acute periarticular fibrositis. Results were variable in the osteoarthritis patients but in 1 with control on drug, exacerbation was said to occur on placebo. Results in gout fair to good (usually the latter). Lab. tests consisted mainly of hemograms and urinalyses. A few patients developed mild to moderate anemia. No stool guiacs done.

32. Scherbel—Uncontrolled study in 21 adults with R.A. or rheum. spond. (16), osteo. (4), neuritis (8), bursitis (1) and miscellaneous conditions. (Some patients had more than 1 diagnosis, therefore the discrepancy in the above totals.) The pts. were given 50 to 200 mg./d. for a few weeks to over 6 months. Results were good in 14, fair in 6. Most pts. received no concomitant therapy. The usual side effects were seen. A few pts. showed a mild rise in BUN. Results in the few cases of osteo. were generally good.

33. Smyth—Uncontrolled study in 27 adults, 1 child (25 with R.A., 2 with acute gout) given less than 50 to 300 mg./d. for a few days to over a year. Concomitant therapy was received by a number of patients. Results were good in 20, fair in 6. Of 4 on steroids, 3 were able to discontinue or decrease dosage. The usual side effects occurred. The 2 patients with acute gout responded well. The wife of a patient on drug delivered a malformed fetus 4½ months old. The mother, however, had been given Thorazine and Bonamine for hyperemesis gravidarum. Five patients had a rise in alk. PO_4ase, 1 a transient rise in SGOT (Still's disease, rise probably not drug-related) and a few showed mild rises in BUN.

34. Thompson—Uncontrolled study in 26 adults with R.A. or rheum. spon. (24), osteo. (4) and several miscellaneous conditions given less than 50 to over 300 mg./d. for a few weeks to over 6 months. Most were on concomitant therapy. Results were good in 12, fair in 3. The usual side effects occurred. In addition, there was 1 case of skin rash beginning 3 weeks after drug was stopped.

Of 7 on steroids, 4 discontinued or decreased dosage. Lab. tests revealed many with positive stool guiacs. One pt. had a decrease in PSP excretion noted after 1 month with no follow-up. Two patients developed a moderate anemia, another a severe anemia (pos. stools, no report of overt bleeding). One pt. developed a severe leukopenia (1500) one month after drug started. She had a mild leukopenia prior to drug. Since she was also on gold salts, the blood dyscrasia may have been due to the gold. When indomethacin was withdrawn, WBC increased to 2600 but no further follow-up could be obtained.

In a detailed case report on 1 of the pts. the investigator stated that this pt., who was on gold salts plus steroid, was also given placebo b.i.d. and responded so well that placebo was decreased to 1/d. She was later switched to indomethacin from placebo.

35. Wallace—Uncontrolled study in 12 adults with R.A. (5) osteo. (8), gout (2) given 50 to 200 mg./d. for up to 4 months. Good results in 6, fair in 2. Usual side effects noted.

36. Ward—Study in 50 adults with R.A. (45), osteo. (5) and miscellaneous disorders given 50 to over 300 mg./d. for a few weeks to over a year. Most were on concomitant ASA and steroids. Good results in 27, fair in 7. There was a high incidence of side effects including 3 cases of mental confusion. Of 32 on steroids, 11 discontinued or decreased dosage. A number of the R.A. pts. were involved in a double-blind crossover study with drug (200 mg./d.) and placebo given for 1 month each. Following this, all were placed on long-term drug therapy. Subjective and objective studies were done. In only a few pts. were striking differences noted between drug and placebo. (The investigator's description of

his results was much more optimistic.) Lab. tests (besides some cases of anemia due to G.I. bleeding) revealed a number of pts. with elevations of alk. PO_4ase. However, some pts. with elevated levels pretreatment showed no worsening or a return to normal during therapy. A few patients showed a mild rise in BUN, usually with return to normal while still on drug.

37. Ziff—10 patients with R.A. treated for up to 2 weeks. This brief duration does not lend itself to meaningful results.

38. Zimmerman—Uncontrolled study in 29 adults (27 with R.A., 2 with rheum. spond. and 1 with osteo.) given 50 to over 300 mg./d. for a few weeks to over a year. None were on concomitant steroids or ASA; 6 received gold salts. The usual side effects were noted. Good results were seen in 9, fair in 7. Lab. tests revealed a few cases of elevation of alk. PO_4ase and ceph. floc. (usually transient), 1 transient elevation of SGOT. No effect on BUN. In a patient with a history of leukopenia and anemia from phenylbutazone, possible early leukopenia was noted with indomethacine (WBC 4,000). Drug was promptly withdrawn.

F. Case reports—Capsules

1. Atkinson—4 patients with R.A. Nothing unusual.

2. Berkowitz—1 patient with acute gout relieved in 24 hours by 150 mg.

3. Bilka—Uncontrolled study in 69 adults with R.A. (66), rheum. spond. (7), bursitis (2), osteo. (1) given 50 to 250 mg./d. in 3 or 4 divided doses for usually up to a month (25) or over 6 months (24). Most had been on the tablet before. Many received concomitant antiarthritic therapy. The usual side effects were prominent but there was only 1 reported case of peptic ulcer. One patient developed localized ileitis. Results were good in 29, fair in 20. Of 19 on steroids, 6 were able to decrease or discontinue dosage. Some patients when switched from tablets to capsules had decrease in side effects. Lab. tests revealed a leukopenia (neutropenia) in the same pt. as reported in the tablet study by this investigator. He stated that this pt. was subsequently removed from therapy and the leukopenia persisted. Another pt. developed mild leukopenia with improvement when drug was with withdrawn. BUNs were O.K. Two pts. had mild rise in SGOT (trainsient in 1, no follow-up in the other).

4. Blechman—Uncontrolled study in 15 adults with R.A. or rheum. spond. (12), osteo. (2) given 50 to 300 mg./d. for, in the majority of cases, less than 5 weeks. Good results in 5, fair in 4. Incidence of side effects high. The 2 patients with osteo failed to respond.

5. Brown—Uncontrolled study in 34 adults, 1 child, with R.A. or rheum. spond. (23), gout (3), bursitis (4), osteo. (1), tendinitis (2), Reiter's syndrome (2) and other miscellaneous disorders given 50 to 200 mg./d. for a few weeks to, in 1 case, over a year. Most were on concurrent ASA or steroids. Side effects were not as common as in some other studies. Results were good in 24, fair in 7. Steroids discontinued or decreased in 5 of 11. The pts. with bursitis were treated for chronic pain rather than acute. All received concomitant ASA. Results were generally good. Lab. tests revealed a few slight rises in alk. PO_4ase and 1 transient rise in BUN.

6. Calabro—Uncontrolled study in 26 adults with R.A., or rheum, spond. (25), Reiter's syndrome (1) given 50 to 150 mg./d. for a few weeks to over a year. Many were on concomitant therapy. Side effects less frequent than in some other studies. No peptic ulcer. Results good in 13, fair in 8. Steroids decreased or discontinued in 2 of 3. Many of the pts. were switched from the tablets to the capsules. Many pts. had positive stool guiacs, 1 had transient increase in SGOT, a few had transient rises in BUN or ceph. floc.

There are many more reports but further detailing will not be done. Only portions that deserve special comment will be discussed hereafter.

Clark had a number of pts. who were switched to placebo and developed exacerbations. One of his pts. had 4 episodes of severe epistaxis while on drug. (No specific work-up was done.) Cramer had 1 pt. who had been on steriods but was removed from steriods before starting indomethacin who developed massive G.I. bleeding after 10 days of drug and ultimately died post-op. from a pulmonary embolus. The pt. had had a gastric ulcer a few years before. David treated 11 patients with osteo. in an uncontrolled study. Results were good in 8. Previously these 11 had been in a group of 20 who had been on tablets and who all obtained good results. Most of Engleman's pts. (23) had been switched from tablets to capsules. Lab. data were given for both tabs. and caps. Many showed transient fluctuations in ceph. floc. and a few in BUN. Englund studied 172 pts. (uncontrolled) including a few children. Of the total, 158 had R.A. or rheum. spond. The incidence of side effects was high in that almost half complained of headache. There was only 1 recorded case of peptic ulcer despite the fact that 108 were on concomitant steroids (31 also on ASA, 25 on phenylbutazone). There were a number of patients who developed anemia, however, and this could have been due to bleeding peptic ulcer, undiagnosed. In an addendum to his report, the investigator stated, in a letter, the perforation of peptic ulcer and bleeding of an ulcer, were seen in a total of 3 cases whose reports were not included in the NDA. Results were reported as good in 153, fair in 7. The high incidence of good results is surprising, to say the least. Although it is not stated, most if not all of these pts. were probably transferred from the tablets. (This investigator's reports on tablet studies are not in the NDA.) A few patients with chronic gout did very well on drug. Five of these, who had averaged 1–3 acute attacks/month for years had had no acute episodes over a 10–12 month period. Some of these patients after awhile only took indomethacin at the earliest sign of acute attacks and were able to abort them. One patient with Still's disease was said to show petechiae at 75 mg./d. which disappeared at 50 mg. No concomitant steroids were given but patient was on gold at the time. No pertinent blood studies were done. Lab. tests revealed fluctuations in alk. Po$_4$ase, T.T. and ceph. floc. in some pts. BUNs not affected.

Grossman (Burton) reported a case of alopecia while on drug (no details). Grossman (Lawrence) reported a case of ulcerative stomatitis. Gum found that using a lower dose of capsules in patients who had been on higher doses of tablets caused a decrease in side effects but also a decrease in effectiveness. One investigator mentioned that several of his patients noted that ingestion of coffee, alcohol or Coca-Cola while they were on drug appeared to precipitate headaches. A few of Kerby's patients had a transient leukopenia. A few had transient elevations of T.T. Some of Kuzell's patients showed a rise in BUN and alk. PO_4ase. (One pt. had marked rise in alk. PO_4ase to 42 K.A. units with drop while still on drug but still at abnormal levels; other liver function tests O.K.) LaTona reported an uncontrolled study in 99 patients (69 with osteo., 14 with miscellaneous musculoskeletal conditions, 12 R.A. or R.S., 7 gout). He was impressed with the results in oseto. (good results in 36 of 66 classied) and gout (good results in 5 of 7). One of his pts. developed syncope while on drug. Lockie reported good results in 8 of 8 patients with oseto. in an uncontrolled study. All of these had no or at best fair results with ASA, phenylbutazone and I.A. steroids. Mahoney reported a case of thrombophlebitis developing after 2 weeks of indomethacin in a pt. with R.A. Massell reported 1 case of acute Still's disease treated for 3½ weeks with indomethacin who, 3 weeks after drug withdrawal (because of poor response), developed severe agranulocytosis with return to normal levels after 10 d. This was not felt to be due to the indomethacin because of the 3 wk. time interval between drug withdrawal and first appearance of leukopenia. Needles placed 1 of his 14 pts. on placebo for 4 wks. and got good results. This pt. had a diagnosis of vertebral osteo. and R.A. of the hands. She had been on dexamethasone 1 mg./d. which was discontinued when placebo was started. Norcross, in a large uncontrolled study in which most of the pts. had ben switched from tablets to capsules, reported ability to lower the total dosage when capsules were used. In addition, there were fewer side effects. Lab. tests revealed no abnormality of liver function, hemograms or urines relative to indomethacin therapy. A few pts. had mild rise in BUN but this was much less frequent than on tablets. Some pts. with elevated levels prior to switch to capsules returned to normal on capsules. In his uncontrolled studies Norcross found 75–80% incidence of improvement in pts. with osteo. In a large series studied by Payne incidence of side effects was high. One of his pts. had leukopenia (3,200) after 3 mos. of drug with no comment and no follow-up. In Phillips' studies 1 pt. developed apparent angioneurotic edema after 2 wks. on drug. Plotz reported again on this pt. who developed leukopenia after approx. 18 mos. of indomethacin. Borderline leukopenia was noted in 2 additional pts. (3,800–3,900) with no follow-up. A few of Plotz' pts. had intermittent elevations of alk. PO_4 ase or BUN.

One of Rosebaum's pts. died of perforated diverticulum after about 4 mos. of therapy. Intermittent BUN or alk. PO_4ase elevations seen in a few.

Rosenberg reported on 15 pts. (8 of whom had osteo., 6 R.A., 1 scleroderma). Only 1 noted pain relief.

Rothermich, in a large series of pts. on capsules, had a high incidence of side effects. One pt. had a marked rise in BUN but at the same time had severe anemia and positive stool guiac so that BUN rise may have been due to G.I. bleeding. (However, unless it was acute and marked the BUN would not rise to such a high level.) The investigator did not mention any appearance of melena in this pt.; he just stated the possibility of bleeding from an ulcer. Another pt. developed leukopenia (3,500) after 6 mos. of drug but no follow-up was done. One pt. had rectal bleeding felt to be possibly coming from a diverticulum. A few pts. had transient BUN elevations. Scherbel reported a decrease in G.I. symptoms with capsules as opposed to tablets. A few of his pts. had elevations in ceph. floc., alk. PO_4ase (marked in some) and BUN. Two pts. with leukopenia (3,000 and 3,600) prior to treatment showed no worsening after 2 mos. of therapy. One of Sidbury's pts. (R.A.) showed rise in SGOT noted after 7 mos. of therapy. There was no follow-up and no other liver function tests were done. Silberman reported a few cases of Hodgkins disease in which indomethacin was employed in an attempt to control hyperpyrexia non-responsive to the usual therapy and good results were noted in most. A few of Smyth's pts, showed elevations of alk. PO_4ase and T.T. and, in contrast to that seen by others, in several pts. both liver function tests were abnormal in the same pt. A few pts. also showed elevations of BUN. Ziff reported 1 pt. who had a marked increase of his Parkinsonism while on indomethacin for osteo. requiring increase in his dosage of diphenhydramine. This controlled the symptoms. One of his pts. reported facial paresthesias on drug. Zimmerman found no greater tolerance to the capsules than to the tablets.

G. Studies in Acute Musculoskeletal Conditions

These were blind studies only in the sense that the investigators and the pts. did not know which dosage was being given. Dosage was 75 or 150 mg./d. x 7 d. to a total of 150 adults. Of the 81 pts. originally started on 75 mg./d. 16 were were dropped, mainly because of side effects. Of the remainder, 44% showed varying degrees of relief from pain on drug and 42% showed increased mobility of the affected part. Of the 69 started out on 150 mg./d. 18 were dropped because of side effects. Of the remainder, 76% showed some degree of pain relief and 40% increased mobility. No code is given prior to the individual case reports so that the reviewer is unable to determine which pts. received which dosage and, therefore, cannot confirm the company's results cited above. The side effects consisted mainly of G.I. distress, headache, dizziness. Two pts. complained of blurring of vision but they had had this on previous occasions unrelated to this drug. With regard to the results, review of the raw data reveals that there were quite a few pts. who had no pain at all at the start of the study (although they had limitation of motion). We would like to know how these pts. were tabulated with regard to pain relief. A large percentage of the studies were done by 1 investigator who used the same dosage (judging from the lot no.) in most of the pts. This investigator obtained the best results. He may have been unconsciously biased into using this lot almost exclusively because of initial improvements noted in the first few pts.

H. Analgesic Studies—Some were controlled

1. Batterman—118 pts. given various dosage forms in an uncontrolled study for a variety of painful conditions (osteo., R.A., pylorospasm, peptic ulcer, cystitis, pharyngitis, headaches etc.), Most were treated for at least 2 weeks. At a 30–40 mg./d. dose level (21 pts.) 66% experienced pain relief or improvement. Of those on 75–100 mg./d. (33), 68.5% reported good results. Most pts. received 150–200 mg./d. (79). Results were good in 51% of this group. The incidence of side effects was as great in the lowest dose group as in the highest but the effects were more severe in the highest dose group. Many of the pts. with G.I. pain reported relief.

2. Cass—Double-blind crossover involving pts. with chronic moderate pain (headache, osteo., P.V.D. etc.) given daily for 6 days, 150 mg. indomethacin, 225 mg. indomethacin, 195 mg. dextropropoxyphene, 1.8 Gm. ASA, 180 mg. codeine or placebo. Dosage was q.4h. x 3 doses/d. only. Degree of pain was recorded daily before the first dose and 1 hr. after each dose. Of 60 pts. started on the study (in a hosp.), 19 were dropped (8 transferred to another hosp. or discharged, 11 refused to continue). (The reasons for dropping out are not given but it is noted that more pts. dropped out during the indomethacin and dextropropoxyphene weeks than during placebo, ASA and codeine. Probably not significant, however.) The overall results will be presented below. However, we are particularly interested in determining the results in osteoarthritis since thhe NDA so far has presented no really controlled data in this condition. There were 5 pts. with this diagnosis. Of these, 2 dropped out the first wk., 1 at the 5th wk. This last pt. and the 2 remaining through the study showed: Pt. 1 obtained about the same pain relief score with placebo and 150 mg. indomethacin, much less relief with 225 mg. indomethacin and pronounced relief with codeine; pts. 2 and 3 obtained significantly

better relief with all agents over placebo, the best results being obtained with dextropropoxyphene and codeine. Overall results reveal the following in decreasing order of effectiveness: codeine, dextropropoxyphene, indomethacin large, indo. small, ASA, placebo.

3. Diamond evaluated indo. 75–100 mg./d. or 150–200 mg./d. and phenylbutazone 300 mg./d. in 3 gps. of pts. (total of 57). This was not a blind study except that he did not know which was the higher and which the lower dose of indo. Results were about equal in the 3 gps. (50% good). Pts. had acute and chronic musculoskeletal conditions.

4. Kast—Studied the effect of placebo, 60 mg. codeine and 300 mg. indomethacin on experimental and pathologic pain using a double-blind procedure. Results were based on a single-dose only. Pain was measured at 1, 2 and 3 hrs. after drug. A significant difference of codeine and indomethacin from placebo was noted only at the 2 and 3 hr. levels.

5. Lamphier—100 pts. with various miscellaneous musculoskeletal pains most of which were not casually diagnosed, being described as low back pain, pain in shoulder, arm, hip headache, etc., were given ASA, dextropropoxyphene or indomethacin (150 mg.) in a double-blind manner for about 2 wks. The response was variable. The indomethacin gp. fared slightly better with regard to pain relief than the other 2 gps. but the difference was not significant.

6. Mandarino—Uncontrolled study in 159 pts. with various musculoskeletal disorders given 150 to 200 mg./d. for usually 2–3 wks. Improvement was reported in 78%.

7. Mullin—Double-blind crossover study in a small number of pts. revealed that indomethacin in a dose of 50 mg. q.i.d. was almost equipotent in analgesic relief to dextropropoxyphene in a dose of 65 mg. q.i.d. Before the pts. were switched from 1 drug to the other they were on placebo for 2 d. and reported little or no pain relief during this time. In another study he demonstrated little analgesic effect from single doses of indomethacin of 20 or 30 mg., however, when indomethacin was given in doses of 25 mg. q.i.d. for 1 d. there was a progressive analgesic effect during the day, possibly due to a cumulative effect.

8. Sunshine—Hospitalized pts. with moderate to severe pain were given ASA 600 mg., indomethacin 50 mg., or placebo at at least 3 hr. intervals in double-blind fashion. All drugs were randomized for each pt. Results for the first dose (92 pts.) revealed greater pain relief with ASA and indomethacin than with placebo. (ASA gave slightly better relief than indomethacin). Results for the second dose (72 pts., since some were dropped if they could not wait 3 hrs. for the next dose or if they had no pain) revealed no difference between placebo and drugs. For the 3rd dose (56 pts.) ASA did slightly better than placebo and indomethacin and of the latter 2, placebo did slightly better than indomethacin.

I. Antipyretic effect

A number of investigators studied the antipyretic effect of 0.5 or 1 mg./kg. of indomethacin in children and found fair to good results. (The higher dose gave better results, usually.)

J. Foreign reports

In general, results from abroad paralleled those seen in the U.S. There was also a high incidence of side effects, including G.I. bleeding (with, in 1 case, shock) and perforation of peptic ulcers. Bagnall, in a letter, reported mild elevation of NPN in some pts.

Bassiouni found good results in pts. with R.A. However, in a child with ulcerative colitis and arthritis, the latter improved considerably but the symptoms of her colitis became more severe requiring withdrawal of drug. One of his pts. developed psychotic-type reactions. Berrios reported photophobia in 2 of 9 pts. One of Carlson's pts. developed leukopenia (3,200) with no follow-up done. Many of Catoggio's pts. developed anemia, 1 had overt melena and hematemesis. Edema was also a common finding. Some pts. had stomatitis. Intermittent increases in NPN were noted and 1 pt. died in uremia with no previous evidence (lab. wise) of renal disease early in the study. Whether this pt. had a past hist. of renal disease is not known. Relationship of her terminal episode to drug, if any, cannot be conjectured. Lindqvist reported G.I. bleeding and ecchymoses in 1 patient. Lovgren (Sweden) reported a high incidence of peptic ulcer in his indomethacin-treated pts. One pt. with multiple gastric ulcers died after gastric resection and another with a large single ulcer died in shock due to uncontrollable hemorrhage (reported in Brit. M.J. Jan 11, 1964). One of Makisara's pts. developed leukopenia (3,100) with no follow-up. Michotte reported G.I. bleeding and intestinal infarction in 1 pt. who had been on steroids for over 10 yrs. and was then withdrawn from steroids, given corticotropin for a few wks. and placed on indomethacin. The pt. had been on indomethacin for 10 d. before the G.I. episode occurred. The possibility of mesenteric artery thrombosis from the steroid therapy cannot be eliminated. Rubens-Duval reported 1 case of decrease in platelets to 130,000 after 6 mos. of therapy with no sign of bleeding. One pt. with a platelet count of 160,000 prior to indomethacin had a count of 220,000 after 1 or 2 wks. of drug. Most of his pts. had low prothrombins prior to therapy and in many of these further reductions occurred. In the others, the levels remained about the same or rose.

Schichikawa reported facial edema as a side effect. This has been reported by other foreign investigators. One of Thompson's pts. reported blurring of vision. Ballabio reported that of 9 pts. tested none showed significant changes in PSR excretion, 3 of 11 had slight abnormalities in creatinine clearance, 2 of 34 had slight rise in BUN (no details given).

Dixon reported, in a paper, on a double-blind crossover trial in 18 pts. with osteo. of the hip given placebo for 4 wks. and increasing doses of indomethacin for 4 wks. (75, 100, 150, mg./d. for weeks 1–4. Pts. were asked to report on effort pain and rest pain. In addition ranges of hip movement were measured. For relief of effort pain 14 of 18 preferred indomethacin. For the relief of rest pain 12 of 16 preferred indomethacin (2 had no rest pain). In 13 pts, the intermalleolar distance was improved 1 inch or more (average 3½ inches) while on drug as compared to placebo. Rotation and flexion of the hip jts, were not significantly affected. No significant changes were noted in NPN. The raw data for this study are not in the NDA. (We called Dr. Shaffer of MSD on 11/23/64 to ask him to send them in). This same investigator reported, in a paper, on 43 pts. with R. A. given indomethacin. One pt. developed a perforated gastric ulcer and another massive G.I. bleeding (no obvious ulcer noted on laparotomy but stomach was not opened.)

Kelly, in an uncontrolled study, reported spectacular results in many pts. with R. A. or osteo. A number of them had evacerbations of pain after a few days, however, so that placebo effect was probably an important factor.

Lapin, in a double-blind study in pts. given indomethacin or placebo for R.A., R.S., osteo. and miscellaneous musculoskeletal conditions reported the following: Of 12 pts. on drug 75% improved (50% good, 25% fair) : of 11 pts. on placebo 54% improved (18% good, 36% fair). Of the group. 3 of 3 pts. with osteo. on drug improved, whereas 3 of 7 pts. with osteo. on placebo improved. However, an analysis of the raw data reveals the following: 10 pts. on drug could be evaluated; of these, 70% improved (30% good, 40% fair) ; 9 pts. on placebo could be evaluated: 66% improved (44% good, 22% fair). There was 1 pt. with osteo, on drug and response was fair. There were 6 pts. with osteo. on placebo; 2 had good results. 1 fair. Accordingly, no conclusions can be drawn from this study.

One of Thompson's pts. apparently developed confusion while on drug and took 5x25 mg. capsules within 3 hrs. He became stuporous for a period of 24 hrs. (Some pts. have been treated with 100 mg. doses without incident so that this pt. was apparently hypersensitive to the drug.) Another of his pts. developed 3 episodes of Jacksonian epilepsy during 5 weeks of drug therapy.

K. Published reports

There are a number of papers in the NDA concerning use of indomethacin. In addition, there are several others that I reviewed that were published since submission of the NDA. Pertinent comments follow for some of the papers:

1. Boland, E.W.—Nonspecific Anti-Inflammatory Agents. Some Notes on Their Practical Application. Especially in Rheumatic Disorders. Calif. Med. 100: 145. 1964. His experience in osteo., chronic tendinitis and bursitis disappointing and most of these pts. noted no difference between drug and placebo. Good results in rheumatoid spondylitis. Inconclusive results in R.A.

2. Hart, F. D.—Indomethacin: A New Non-Steroid Anti-Inflammatory Agent. Brit. M.J. 2: 965, 1963. He reported drowsiness in a pt. 10 min. after ingestion of a 100 mg. dose with severe headache following shortly thereafter. (N.B. Single doses at this level are not recommended in the labeling.) Drowsiness accompanied by blurring of vision was noted in 2 more of his pts.

3. Lovgren, O. and Allander, E.—Side Effects of Indomethacin, Brit. M.J. 1: 118, 1964. They reported on the incidence of gastric and duodenal ulcers in

their pts. including the death due to massive hemorrhage and the death after gastric resection (See Case Reports section on previous pages.)

4. Wanka, J. et al.—Indomethacin in Rheumatic Diseases. A Controlled Clinical Trial, Ann. Rheum. Dis. 23: 218, 1964—G.I. hemorrhage in 1, perforated peptic ulcer in 1, tinnitus in 4; 1 pt. had positive Romberg and ataxia on 1 occasion.

L. Addenda

(1) In response to our request concerning data on controlled trials in acute musculoskeletal disorders the company submitted the following (which it had received after submission of its NDA):

(*a*) Uncontrolled case reports.

(*b*) Table of controlled studies using indomethacin and carisoprodol. Both gave equally good results. There was no comparison with placebo.

(2) The company submitted some new adverse reaction reports:

(*a*) Another 2 deaths due to sudden G.I. hemorrhage (pts. were also on prednisone). These were reported by Michotte of Belgium. In a total of 70 pts. receiving indomethacin, besides the above 2 incidents, he had 1 case of bleeding from a gastric neoplasm; 1 perforated ulcer; 4 more peptic ulcers, 1 with melena; and 1 case of bleeding from the sigmoid.

(*b*) Report that a paper was presented in Belgium recently by Dixon on decreased creatinine clearance in some of his pts. on indo. There are no details.

(*c*) Report of a pt. with epilepsy controlled by diphenylhydantoin who developed severe epileptiform convulsions after 5 d. on indo. with no recurrence when indo. was withdrawn.

(*d*) Report of a pt. who died in hypoglycemic shock while taking 225 or 450 mg./d. of indo. instead of 75 or 150 mg. as had been prescribed. There are no details on this case and, in view of the uniform lack of effect of indo. on blood sugars this episode is probably unrelated to this drug.

(*e*) Report of impairment of vision in an elderly male who had been on indo. for 6 wks. No ophthalmologic exam. done.

(*f*) Report of chronic granulomatous and ulcerative colitis occurring in a pt. without previous history of G.I. disease who had been on indo. for 10 mos.

(*g*) Report of a case of hepatitis in a pt. who had been on indo. for 1 yr. prior to onset of symptoms of hepatitis. He had had several blood transfusions 3½ mos. before. It appears that the hepatitis is unrelated to the drug since he had been taking it for 1 yr. with no incident.

(*h*) Report of unilateral blurring of vision which had begun 6 mos. prior to institution of indo. therapy. Ophthalmoscopic exam. (probably not by ophthalmologist) was neg. at time of beginning indo. Exam by an ophthalmologist 8 mos. after onset of indo. therapy revealed early optic atrophy.

(*i*) A report was submitted in the IND concerning a case of agranulocytosis occurring 3 d. after starting indo. The details of this report do not permit a definite conclusion concerning the culpability of the drug but it appears quite possible that the drug was not related to the episode.

M. Labeling

1. Under Clinical Indications, "acute inflammatory musculoskeletal disorders" on page 1 should be specifically defined, inasmuch as on page 3 only acute bursitis, synovitis, tenosynovitis, and tendinitis are listed, whereas most clinicians usually also include myositis and fibrositis. However, the indications approvable at this time are limited to rheumatoid arthritis, rheumatoid spondylitis and gout (See Conclusions, below).

2. On pages 2 and 3, the discussions under osteoarthritis, degenerative joint disease of the hip, and acute bursitis, synovitis, tenosynovitis and tendinitis should be deleted.

3. On page 2 under "Rheumatoid Spondylitis", "frequently" should be substituted for "usually" and the words "in most patients" should be deleted.

On page 2 under "Gout," second sentence, "is usually" should be deleted and "may be" substituted. On page 3, second pargraph, "may be" should be substituted for "usually".

4. Contraindications should be revised and considerably expanded, as follows: "As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration. For these reasons etc. etc. Inasmuch as this drug may cause irritation of the gastrointestinal tract, it is also contraindicated in patients with gastritis, ulcerative

colitis and regional enteritis. Indocin is contraindicated in patients with renal disease, psychosis or marked emotional instability, and central nervous system diseases such as epilepsy and parkinsonism. It is also contraindicated in patients with a history of blood dyscrasia.

"Reproduction studies in mice, rats and rabbits showed no effect on fetal development or on the reproductive cycle, although, in rats, there was some decrease in fetal viability. However, since studies in mice demonstrated that this drug crosses the placental barrier and since severe adverse reactions have been noted in some adults, this drug should not be given to pregnant patients.

"Indocin should not be administered to children."

5. The discussion under Warning relating to pregnancy should be deleted, inasmuch as this is to be placed in "Contraindications," and the following inserted:

"Since dizziness and lightheadedness are frequent side effects during indomethacin therapy, patients should be cautioned against operating motor vehicles or other machinery, climbing ladders etc. in the presence of these symptoms."

6. "Side Effects and Precautions" should be altered to "Precautions and Adverse Reactions." Considerable revision and expansion are required.

(*a*) The first paragraph should be revised to: "Headache, dizziness and lightheadedness frequently occur as a result of Indocin therapy. Onset is usually early in the course of treatment. Starting treatment etc. etc. These symptoms frequently disappear" etc. etc. The word "rarely" should be deleted from the next to the last paragraph on page 3 and, "on occasion" be inserted after "require."

(*b*) The submitted labeling strongly implies that the gastrointestinal side effects of this drug are infrequent and minor in nature. Since this is patiently not the case, we recommend that the following be substituted for the last paragraph on page 3 and the discussion on the first half of page 4: "Indomethacin may cause ulceration, single or multiple in nature, of the stomach, duodenum or small intestine. There have been reports of massive bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, Indocin should be discontinued. In many of the patients with peptic ulceration, there has been a history of peptic ulcer or patients have been on concomitant steroids, salicylates or phenylbutazone. Possible potentiation by indomethacin of the ulcerogenic effect of these compounds cannot be ruled out at present. However, in some cases there was no history of a previous peptic ulcer and other drugs were not being given. Reports of bleeding from the sigmoid colon with no known previous pathology, or bleeding from a sigmoid diverticulum have been received. Many patients develop occult gastrointestinal bleeding and, as a result, a few may manifest mild to moderate anemia. Periodic hematocrit and hemoglobin determinations are recommended in all patients receiving Indocin. Studies in normal volunteers with radioactive chromate-tagged red blood cells etc. etc.

"Perforation of sigmoid lesions (diverticulum, carcinoma) have been reported rarely in patients on indomethacin. A diagnosis of gastritis has been made in some patients at laparotomy. The occurrence of ulcerative colitis and regional enteritis has been reported in one patient each; and pre-existing ulcerative colitis has worsened in one patient on Indocin. It is not known whether these intestinal lesions can be attributed to indomethacin.

"Milder gastrointestinal disturbances (e.g., anorexia, nausea, vomiting, diarrhea or epigastric discomfort) are not uncommon."

(*c*) Urticaria and angioneurotic edema should be added to side effects.

(*d*) The possible exacerbation of epilepsy or parkinsonism or the occurrence of convulsions in patients on drug should be mentioned.

(*e*) On page 4, in the sentence beginning "A slight and transient increase" etc. the word "usually" should be substituted for "and" and "some" for "few." After the end of the paragraph containing this sentence, the following should be added: "Transient elevations in alkaline phosphatase, cephalin flocculation and thymol turbidity levels have been noted in some patients and, rarely, elevations of SGOT values. The relationship, if any, to the drug has not been established."

7. Under Dosage and Administration, osteoarthritis, degenerative joint disease of the hip and acute musculoskeletal disorders should be deleted. On page 7, sentence 2 should be revised to: "Definite relief of pain has been reported within 2 to 4 hours." Also on this page, the following should be added to paragraph 2: "In patients who are relatively comfortable during the interval phase, it may be advisable to withdraw indomethacin and reinstitute it only at the earliest sign of an acute attack."

8. On page 9 the sentence beginning "Controlled clinical studies" etc. should be deleted, inasmuch as other controlled clinical studies have not demonstrated this.

Conclusions

The application is incomplete as follows:

1. Inasmuch as Norcross reported diminution in creatinine clearance and renal plasma flow and abnormalities in renograms in several patients and volunteers on indomethacin; Dixon has recently presented a paper in Belgium, we are told, discussing decrease in creatinine clearance on this drug; and some patients have shown elevations in BUN, we feel that further studies should be performed in patients relative to effect of the drug on renal function.

2. The labeling is grossly inadequate in providing full disclosure of the serious adverse effects of this drug.

3. Although there is a paucity of controlled studies in this massive NDA, it is apparent that many patients with rheumatoid spondylitis and gout and some patients with rheumatoid arthritis receive significant benefit from the anti-inflammatory effects of this drug. The lack of controlled studies prevents adequate evaluation of indomethacin as an analgesic agent in osteoarthritis and degenerative joint disease of the hip. It is possible that where these conditions are accompanied by an inflammatory component benefit may be derived. The high incident of placebo response in these diseases is well known; therefore, in view of the nature of the adverse reactions to this drug, it is mandatory that beneficial effect be established before the drug can be approved for widespread use in these conditions. A controlled study done by Dixon in patients with degenerative joint disease of the hip may shed some light on efficacy, but failure to submit the raw data prevents evaluation of his results. However, one controlled study in a small number of patients is inadequate evidence. We recognize that Cass performed a controlled study on analgesic effect of this drug as well as several others in chronic pain conditions, but in his study the medications were given at intervals of four hours, whereas the labeling recommends b. or t.i.d. dosage. In his study there were only two patients with osteoarthritis who completed the full course of therapy and one who almost did. These patients were on indomethacin for a total of only two weeks. Obviously, no conclusions can be drawn from this. The marked responses in some patients with long-standing osteoarthritis observed by some investigators in uncontrolled studies would appear to be at variance with the supposedly mildly analgesic properties of this drug.

Accordingly, we recommend controlled clinical trials, by several investigators, in patients with osteoarthritis of the hip and other locations. Patients should be classified, when possible, into those with and those without inflammatory components. The lack of controlled studies also prevents evaluation of the usefulness of this drug in acute bursitis, synovitis, tendinitis and tenosynovitis.

We would have no objection to release of this agent (following clarification of the renal effect, if any, and revision of the labeling) for use in rheumatoid arthritis, rheumatoid spondylitis and gout.

MARION J. FINKEL, M.D.

AMENDMENT NDA 16-059

PRODUCT: INDOCIN (INDOMETHACIN) CAPSULES

APPLICANT: MERCK SHARP & DOHME, WEST POINT, PA., AF 4-715, DECEMBER 9, 1964

Submitted Nov. 25, 1964: a copy of Dixon's paper on his 18 pts. with degenerative joint disease of the hip given indomethacin or placebo in a double-blind crossover study. This paper was published in Ann. Rheumat. Dis. 23:288, July 1964 and is expanded over the one submitted in the original NDA. A figure in the paper gives the results in these pts. Unfortunately, the legend does not state which symbols are drug and which placebo. A surmise, however, leads us to the following observations. For relief of effort pain, 7 of the 18 did better on drug. 5 did well on placebo and in 6 there was no response. For relief of rest pain 5 of 16 did better on drug, 7 fared well on placebo and in 4 there was no response. These conclusions, based on the author's figures, are at considerable variance with his own conclusions. In cases in which the patient was obtaining an increasingly good response to placebo and then, when switched to drug, continued to obtain increasingly, good response, the author listed these as doing better on drug, thus providing his excellent figures for drug response. Obviously this is spurious, although it cannot be concluded that these pts. would not actually do better on drug in long-term trials.

MARION J. FINKEL, M.D.

December 23, 1964.

MERCK SHARP & DOHME RESEARCH LABORATORIES,
Division of Merck Co., Inc., West Point, Pa.

Attention Dr. M. Jane Howell.

GENTLEMEN: Reference is made to your new drug application dated June 5, 1964 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "Indocin" (Indomethacin), 25 mg. and 50 mg. capsules.

We also acknowledge receipt of your additional communications dated July 1, 1964, November 13, 1964, November 20, 1964 and November 25, 1964.

The application is incomplete under section 505(b)(1) and (6) of the Act in that the submitted data fail to establish, in certain respects, the safety and efficacy of this drug. In this connection we have the following comments:

(1) Inasmuch as Norcross reported diminution in creatinine clearance and renal plasma flow and abnormalities in renogramps in several patients and volunteers on indomethacin; Dixon has recently presented a paper in Belgium, we are told, discussing decrease in creatinine clearance on this drug; and some patients have shown elevations in BUN, we feel that further studies should be performed in patients relative to effect of the drug on renal function.

(2) Although there is a paucity of controlled studies in this new drug application it is apparent that many patients with rheumatoid spondylitis and gout and some patients with rheumatoid arthritis receive significant benefit from the anti-inflammatory effects of the drug. This essential lack of controlled studies prevents adequate evaluation of indomethacin as an analgesic agent in osteoarthritis, including degenerative joint disease of the hip. It is possible that where these conditions are accompanied by an inflammatory component benefit may be derived. The high incidence of placebo response in these diseases is well known; therefore, in view of the nature of the adverse reactions to this drug, it is desirable that beneficial effect be established before the drug can be approved for widespread use in these conditions. Although, in a small controlled study on osteoarthritis of the hip by Wanka and Dixon, the authors report an overwhelming preference for drug over placebo, a review of Figure 2 in their published paper (Ann. Rheumat. Dis. 23:288, 1964) reveals that for relief of effort pain, 7 of 18 definitely did better on drug, 5 responded nicely to placebo and in 6 there was essentially no response; for relief of rest pain, 5 of 16 did better on drug, 7 fared well on placebo and in 4 there was no response. Although it cannot be concluded that a number of the patients would not have had a greater response to drug than placebo in long-term trials, no conclusions can be drawn from this study.

We recognize that Cass performed a controlled study on analgesic effect of this drug as well as several others in chronic pain conditions, but in his study the medications were given at intervals of four hours, where as the labeling recommends b. or t.i.d. dosage. In his study there were only two patients with osteoarthritis who completed the full course of therapy and one who completed most of it. These patients were on indomethacin for a total of only two weeks. Obviously, no conclusions can be drawn from this. The marked responses in some patients with long-standing osteoarthritis unresponsive to multiple therapeutic regimens observed by some investigators in uncontrolled studies would appear to be at variance with the supposedly mildly analgesic properties of this drug.

Accordingly, we recommend controlled clinical trials, by several investigators, in patients with osteoarthritis of the hip and other locations. Patients should be classified, when possible, into those with and those without inflammatory components.

The lack of controlled studies also prevents evaluation of the usefulness of this drug in acute bursitis, synovitis, tendinitis and tenosynovitis and, again, we recommend the performance of adequate trials in these conditions.

The application is further incomplete under section 505(b)(1) and (6) of the Act in that the proposed labeling fails to provide adequate information whereby practitioners licensed by law may safely use this preparation. We recommend that the package and direction circular be revised as follows:

(1) Under Clinical Indications, "acute inflammatory musculoskeletal disorders" on page 1 should be specifically defined, inasmuch as on page 3 only acute bursitis, synovitis, tenosynovitis, and tendinitis are listed, where as most clinicians usually also include myositis and fibrositis. However, as noted above, the indications approvable at this time are limited to rheumatoid arthritis, rheumatoid spondylitis and gout, pending satisfactory completion of item #1 on first page of letter.

(2) On pages 2 and 3, the discussions under osteoarthritis, degenerative joint disease of the hip, and acute bursitis, synovitis, tenosynovitis and tendinitis should be deleted.

(3) On page 2 under "Rheumatoid Spondylitis," "frequently" should be substituted for "usually" and the words "in most patients" should be deleted.

On page 2 under "Gout," second sentence, "is usually" should be deleted and "may be" substituted. On page 3, second paragraph, "may be" should be substituted for "usually."

(4) Contraindications should be revised and considerably expanded, as follows:

"As with other anti-inflammatory agents, Indocin may mask the signs and symptoms of peptic ulcer. Indocin may itself cause peptic ulceration. For these reasons, etc. etc. Inasmuch as this drug may cause irritation of the gastrointestinal tract, it is also contraindicated in patients with gastritis, ulcerative colitis and regional enteritis. Indocin is contraindicated in patients with renal disease, psychosis or marked emotional instability, and central nervous system diseases such as epilepsy and parkinsonism. It is also contraindicated in patients with a history of blood dyscrasia.

"Reproduction studies in mice, rats and rabbits showed no effect on fetal development or on the reproductive cycle, although, in rats, there was some decrease in fetal viability. However, since studies in mice demonstrated that this drug crosses the placental barrier and since severe adverse reactions have been noted in some adults, this drug should not be given to pregnant patients.

"Indocin should not be administered to children."

(5) The discussion under Warning relating to pregnancy should be deleted (inasmuch as this is to be placed in "Contraindications") and the following inserted:

"Since dizziness and lightheadedness are frequent side effects during indomethacin therapy, patients should be cautioned against operating motor vehicles or other machinery, climbing ladders etc. in the presence of these symptoms."

(6) "Side Effects and Precautions" should be altered to "Precautions and Adverse Reactions." Considerable revision and expansion are required.

> (*a*) The first paragraph should be revised to: "Headache, dizziness and lightheadedness frequently occur as a result of Indocin therapy. Onset is usually early in the course of treatment. Starting treatments etc. etc. These symptoms frequently disappear" etc. etc. The word "rarely" should be deleted from the next to the last paragraph on page 3 and, "on occasion" be inserted after "require."
>
> (*b*) The submitted labeling strongly implies that the gastrointestinal side effects of this drug are infrequent and minor in nature. Since this is patently not the case, we recommend that the following (in effect) be substituted for the last paragraph on page 3 and the discussion on the first half of page 4: "Indomethacin may cause ulceration, single or multiple in nature, of the stomach, duodenum or small intestine. There have been reports of massive bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, Indocin should be discontinued. In many of the patients with peptic ulceration, there has been a history of peptic ulcer or patients have been on concomitant steroids, salicylates or phenylbutazone. Possible potentiation by indomethacin of the ulcerogenic effect of these compounds cannot be ruled out at present. However, in some cases there was no history of a previous peptic ulcer and other drugs were not being given. Reports of bleeding from the sigmoid colon with no known previous pathology, or bleeding from a sigmoid diverticulum have been received. Many patients develop occult gastrointestinal bleeding and, as a result, a few may manifest mild to moderate anemia. Periodic hematocrit and hemoglobin determinations are recommended in all patients receiving Indocin. Studies in normal volunteers with radioactive chromate-tagged red blood cells etc. etc.
>
> "A diagnosis of gastritis has been made in some patients at laparotomy. Perforation of sigmoid lesions (diverticulum, carcinoma) have been reported rarely in patients on indomethacin. The occurrence of ulcerative colitis and

regional enteritis has been reported in one patient each; and preexisting ulcerative colitis has worsened in one patient on Indocin. It is not known whether these intestinal lesions can be attributed to indomethacin.

"Milder gastrointestinal disturbances (e.g., anorexia, nausea, vomiting, diarrhea or epigastric discomfort) are not uncommon."

(*c*) Urticaria and angioneurotic edema should be added to side effects.

(*d*) The possible exacerbation of epilepsy or parkinsonism or the occurrence of convulsions in patients on drug should be mentioned.

(*e*) On page 4, in the sentence beginning "A slight and transient increase" etc. the word "usually" should be substituted for "and" and "some" for "few". After the end of the paragraph containing this sentence, the following should be added: "Transient elevations in alkaline phosphatase, cephalin flocculation and thymol turbidity levels have been noted in some patients and, rarely, elevations of SGOT values. The relationship, if any, to the drug has not been established."

(7) Under Dosage and Administration, osteoarthritis, degenerative joint disease of the hip and acute musculoskeletal disorders should be deleted. On page 7, sentence 2 should be revised to: "Definite relief of pain has been reported within 2 to 4 hours." Also on this page, the following should be added to paragraph 2: "In patients who are relatively comfortable during the interval phase, it may be advisable to withdraw indomethacin and reinstitute it only at the earliest sign of an acute attack."

(8) On page 9 the sentence beginning "Controlled clinical studies" etc. should be deleted, inasmuch as other controlled clinical studies have not demonstrated this.

We have the following recommendations regarding part 4 of the application: We request that you submit to us a description of the buildings in which the manufacturing is to be conducted. From the application it is not clear at what location the milling and blending operations are to be performed. It appears from the application that these will not be undertaken at the West Point plant. In connection with the processing, the types of tableting machines are mentioned but not encapsulating machines which are described only as "standard." We inquire concerning these matters.

With respect to the liquid lecithin concentrate component of the capsule content we request that you submit to us a copy of the protocol of the test results for a lot of this material from A. E. Staley Manufacturing Co., that you have used in the capsule manufacture.

With respect to the market packages of the drug we inquire whether the bottles are flint or amber and, as to the type of closure you propose to use.

In the matter of the package yield we inquire as to the criteria your propose to use in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

With respect to the control procedure that you describe for determining the capsule dissolution rate we recommend that you submit data obtained from such tests for the capsules tested in your stability program and for the lots of capsules submitted to us as samples.

Since the application is incomplete under section 505(b)(1) and (6) of the Act it may not be filed as an application provided for in section 505(b).

Sincerely yours,

MARION J. FINKEL, M.D.,
Medical Officer, Medical Evaluation Branch, Division of New Drugs, Bureau of Medicine.

SUMMARY OF AMENDMENTS NDA 16–059

PRODUCT: INDOCIN (INDOMETHACIN) CAPSULES—MERCK SHARP & DOHME, WEST POINT, PA., AF 4–715, APRIL 30, 1965

1. Amendment dated April 7, 1965 contains FPL. This is approvable with the exception that possible aggravation by indomethacin of emotional disorders, epilepsy and parkinsonism should be moved from "Precautions" to "Warnings."

2. Amendment dated April 22, 1965 contains:

(*a*) A study by Elwood involving I. V. administration of a single dose of 20, 40 or 60 mg. indomethacin to 3 normal subjects revealed a drop in GFR and RPF in the pt. given 60 mg. This was attributed to fright, since at the 40 and 60 mg. doses the subjects noted a generalized warmth and the 60 mg. dose individual "became rigid with fright." The other 2 pts. showed no significant changes.

(*b*) Data from De Martini on 1 pt. with a lung abscess who had received 200 mg./d. indomethacin orally for almost 2 mos. Inulin and PAH clearances prior to drug, after 1 wk. and after 6 wks. on drug revealed no evidence of adverse renal effect.

(*c*) Raw data on Wanka's pts. in whom creatinine clearances were done during therapy and, in some cases, also prior to therapy. The marked fluctuations in determinations make the data valueless. One of the pts. was listed as havng a WBC of 600 and one of 900 after 1½ yrs. and 3 mos. respectively, on drug but we assume these are really 6,000 and 9,000. Counts 1 mo. and 5 mos. later while still on drug were 4,100 and 7,400. Four pts. had transient levels of 3,300, 3,500 and 3,700 with return to normal while still on drug. None were on concomitant medication. There were no differential counts. These transient leukopenias would not appear to be drug-related.

(*d*) Rothermich submitted GFR and RPF studies in 8 pts. On drug for at least 2 yrs. One pt. had a low GFR, 1 a low RPF and 1 low levels of both. The latter pt. was age 63 and the investigator attributes these levels to age. The other 2 pts. were 41 and 42 yrs. old. No control levels were obtained. These 3 pts. had normal BUN's and urinalyses. BUNs and urinalyses are given for 23 additional pts. treated for at least 2 yrs. with no apparent drug-related abnormalities. One of these is a pt. with chronic pyelonephritis who exhibited no worsening of her disease state as based on periodic BUNs, urinary albumin and casts. Pretreatment levels are not given. The pt. had hematuria during most of the drug period. It is assumed that she also had this prior to drug since the investigator commented that there was no worsening of her disease state.

CONCLUSIONS

The data accumulated thus far do not indicate that indomethacin adversely affects renal function. It will be of interest to review the 3 month subacute studies being performed now. My recommendation is that this applicaiton be considered approvable with the stipulation that the FPL contain a Warning statement concerning pts. with epilepsy, parkinsonism and emotional disorders.

An agreement was reached on April 8, 1965 between Dr. Shaffer of MSD and myself that the statement relative to pts. with the above disorders would be moved from "Precautions and Adverse Reactions" to "Warnings".

MARION J. FINKEL, M.D.

MEMO OF (TELEPHONE) INTERVIEW, FEBRUARY 12, 1965—DR. JAMES SHAFFER, MERCK SHARP & DOHME AND DR. MARION J. FINKEL, MEB-DND

SUMMARY OF SUBSTANCE OF CONTACT

Dr. Shaffer stated that some new data supporting efficacy in osteoarthritis of the hip were available. We stated that these were still insufficient to support the claim for osteoarthritis since the drug would be used mainly for the less severe disease, i.e., involvement of the knees, hands, back etc. Although it has never been established, the possibility that malum coxae senilis may have a greater inflammatory component than involvement elsewhere might account for good results noted in this location.

Dr. Shaffer mentioned that Norcross had reexamined his renal data and felt that he had erred originally (as he told me over the phone) in thinking that the drug depressed renal function. Nevertheless, he is now doing 3 month studies, as I requested.

I indicated to Dr. Shaffer that I would go along with release of the drug prior to completion of these studies with immediate revision of the labeling if any adverse effects were obtained.

We also discussed labeling revisions as outlined in our communication to the Company. Dr Shaffer indicated that the labeling was being rewritten.

MEMO OF (TELEPHONE) INTERVIEW, MARCH 1, 1965—DRS. F. D. LAWRASON AND J. M. SHAFFER, MERCK SHARP & DOHME, AND MARION J. FINKEL, M.D., MEDICAL EVALUATION BRANCH DIVISION OF NEW DRUGS/BM

SUMMARY OF SUBSTANCE OF CONTACT

The visitors came to discuss their new data concerning drug effect in osteoarthritis of the hip. They also discussed the labeling and stated that they were reluctant to make regional enteritis a contraindication since indomethacin was being studied in this disease and a few patients appeared to benefit. They preferred to place regional enteritis under precautions. They also wanted to place ulcerative colitis under precautions rather than contraindications.

I disagreed with their ulcerative colitis suggestion. Inasmuch as G.I. ulcerations occurred in rats, dogs, monkeys, rabbits, guinea pigs, cats, pigs and mice and gastric duodenal and small intestinal ulcers in humans, as well as sigmoidal bleeding, it seems reasonable to predict that this drug may have an adverse effect on pre-existing colonic ulceration. With regard to regional enteritis, it may be that this drug could have a salutary effect on the inflammatory nature of this disease. In the presence of mucosal ulcerations, however, it may possibly have an adverse effect. The fact that in one patient with ulcerative colitis given indomethacin the colitis symptoms worsened, and in one patient each colitis and ileitis developed while on drug suggests that this drug may not have a therapeutic effect on the intestine. However, inasmuch as this situation has not been clarified, the drug should probably not be used in patients with these conditions until further evidence is in. The company agreed finally to put ulcerative colitis in contraindications. I agreed to the placing of psychiatric disturbances, epilepsy and parkinsonism under precautions rather than contraindications.

They submitted an amendment to the NDA consisting of data on osteoarthritis of the hip, revised labeling and other material which will be described in my summary of the amendment.

SUMMARY OF AMENDMENT TO NDA 16-059

PRODUCT: INDOCIN (INDOMETHACIN) CAPSULES—MERCK SHARP & DOHME, WEST POINT, PA., AF 4-715, APRIL 5, 1965

1. Amendment submitted Dec. 21, 1964 contains the following pertinent information:

(*a*) Report by R. G. Robinson on 7 cases with severe mental symptoms during indomethacin therapy. These were observed among a total of almost 200 pts. treated during a 2 yr. period. Symptoms consisted of depression in a manic-depressive type patient with suicide due to barbiturate overdosage; fright, nervousness, fear of insanity in another; depression, laziness, inaccuracy in work in 1; depression in 2; depression, fatigue, indifference in 1; history of "nervous breakdown" in 1 requiring E.C.T. Withdrawal of the drug was required in some. A number of pts. were treated with intermittent therapy because of the side effects.

In addition to these, another 22 pts. had milder symptoms consisting of "peculiar feelings", detachments, lack of emotion and well being, lack of drive and energy, melancholia.

The emotional disturbances responded to withdrawal of drug.

In a prepublication manuscript, Robinson noted that his results in osteoarthritis were not very satisfactory and, also, indomethacin had no effect in 6 cases of acute tenosynovitis. He noted a high incidence of headache in his patients.

(*b*) A preprint of a paper by Coste et al. will not be discussed in detail since it adds little to what is already known about indomethacin. He obtained good results in the treatment of headache associated with indomethacin by giving methysergide. These authors also attribued to indomethacin a death due to mesenteric infarction (at autopsy mesenteric vessels reported as "normal") and pulmonary infarction in a patient with polymyositis on long-term corticosteroid therapy and 1 month of indomethacin.

2. Amendment submitted March 1, 1965 contains the following pertinent data:

(*a*) A letter from Norcross stating that he feels his technics for measuring renal functions were faulty and he is repeating them utilizing other methods. It is of interest, however, that decreases were always recorded on drug and no increases. He stated that he has not noted any evidence of renal toxicity in his patients on indomethacin, and in some patients on drug for 2–3 yrs. renal function tests have been unchanged.

(*b*) A copy of the paper by Wanka (coinvestigator with Dixon) discussing his findings with regard to renal function during indomethacin. It will be recalled that in my summary of the original submission I mentioned that a report from the company alluded to a paper that Dixon (and Wanka) had presented in Belgium concerning decreased creatinine clearance in some pts. on indomethacin. I mentioned this in our communication to the company dated January 13, 1965 and in response they submitted a copy of the talk. A review of this paper reveals that it has no value with regard to demonstrating a toxic effect on the kidney, since 4 to 7 control patients showed a moderate to marked decrease in creatinine clearance. Drs. John Laragh and Felix Demartini also felt that the paper did not lend itself to interpretation.

(*c*) It will also be recalled that, in my summary of the original submission, I noted that I had called Dr. Shaffer to request him to send in the raw data on the Wanka-Dixon study in osteoarthritis of the hip. The raw data reveal that of 8 pts. started on drug first for 4 wks. then switched to placebo for 4 wks., 6 obtained an increase in intermalleolar distance with subsequent decline on placebo. In 2 of the 6 improvement only lasted for the initial 2 weeks of drug and in a 3rd, it declined by the 4th week although it was still greater than control levels. Of the 2 pts. who failed to respond to drug, 1 showed a good response on placebo. Of 10 patients begun on placebo for 4 wks. then switched to drug for 4 wks., 5 showed an effect on drug with little or no effect on placebo, although in 1 the improvement had disappeared by the 4th wk. on drug and in 2 it was not manifest until the 4th week. In the remaining 5 pts., 3 improved on both placebo and drug and 2 had no response. A statistical evaluation of the means reports that the effect of drug over placebo was significantly greater at both the 2 and 4 wk. determinations. (P less than 5% and less than 1% respectivey).

(*d*) A reprint of a paper by Michotte and Wanters on their results with indomethacin, reported in Rhumatologie 16:447, Nov. 1964. Results unimpressive in R.A. A few pts. showed a rise in BUN which returned to normal while still on drug or after drug was withdrawn. In 20 pts. with osteoarthritis of the hip the mean values showed an increase in knee separation measurements while on 50 or 75 mg. of drug as opposed to a placebo period and a period on phenylbutazone. There were no side effects because of the low dosage.

(*e*) A paper by Norcross and Latona summarizing their results with indomethacin (publication ?). There is little new in this paper. However, they report that in 12 pts. with osteoarthritis of the hip with failure to respond to bed rest, physiotherapy, analgesics, I.A. steroids or phenylbutazone, improvement occurred on 75–150 mg./d. indomethacin (marked pain relief and moderate improvement in walking). It is not clear from the paper whether all 12 or some of the 12 improved.

This paper reports on 530 patients treated during a 30 month period of drug testing. During the first year of testing it is stated that a rise in BUN to 25–32 mg./100 ml. was observed in 46 pts. (The total number of pts. examined is not stated.) However, during the next year of therapy, the BUNs returned to normal in all but 12. BUN changes were reported less frequently in pts. on capsules as opposed to tablets. Of the 12 pts. with persistent elevations, 5 were studied intensively and found to have had pre-existing renal disease!!

(*f*) A letter from Mendeloff stating that in 3 pts. with ulcerative colitis 2 developed severe abdominal pain after a few days on drug and 1 developed increase in severity of his previously present headaches. In 4 pts. with regional enteritis treated for 10 d. to 1 mo., 3 were stated to have a satisfactory clinical improvement during therapy and a 5th, treated for 6 mos., developed a remission during that period.

(*g*) New control and manufacturing data.

(*h*) Revised package and direction circular. This incorporates most of the changes recommended in our letter of January 13, 1965 and agreed to in discussions with company representatives on Feb. 12 and Mar. 1, 1965.

However, the labeling is still inadequate in certain respects, viz:

1. On page 2, under "Degenerative Joint Disease (Osteoarthritis) of the Hip," the discussion should be revised to: "Indocin has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip."

2. Under "Contraindications" it should be stated that in four patients with regional enteritis treated for up to one month and one patient treated for six months, indomethacin was well-tolerated. However, in view of the paucity of

data this drug should not be given to patients with regional enteritis until additional evidence of gastrointestinal tolerance is available.

3. Under Warning, "feelings of detachment" should be added.

4. On page 4, in the sentence beginning "Notwithstanding, Indocin may cause ulceration" etc., it is noted that the words "single or multiple in nature" have not been inserted following "ulceration", as recommended in our communication of January 13, 1965.

5. It is also noted that the sentence recommended in our January 13 communication—"Patients may also develop gastrointestinal bleeding with no obvious ulcer formation"—has not been inserted.

6. On page 4 the paragraph beginning "Although a few patients with regional enteritis" should be deleted.

7. On page 5, it should be stated that when Indocin was given to patients with ulcerative colitis, there was an increase in abdominal pain.

In a discussion on April 1, 1965 between Dr. James Shaffer of Merck Sharp and Dohme and myself, it was agreed that the above changes would be incorporated in the FPL. Accordingly, this application is conditionally approvable from the medical standpoint.

MARION J. FINKEL, M.D.

MEMO OF INTERVIEW, APRIL 7, 1965—HOWARD D. COHN, M.D., CHIEF, MEB/DND/BM, AND MARION J. FINKEL, M.D., MEB/DND/BM

SUMMARY OF SUBSTANCE OF CONTACT

A discussion was held concerning several points in our January 13, 1965, communication to the company concerning labeling and several incomplete aspects of the NDA.

With regard to a possible adverse effect on renal function, it was agreed to wait for further data from the company. The labeling for the drug now contains the following statements relative to renal function: "Extensive laboratory examinations have been made during treatment with Indocin. A slight, usually transient, increase in BUN has been reported in some patients. Although two investigators have reported apparent changes in renal function, the reliability of the techniques used was uncertain. The preponderance of evidence indicates that Indocin does not have an adverse effect on renal function. Patients with pre-existing renal disease have received Indocin without difficulty."

With regard to the January 13, 1965 recommendation that renal disease, phychosis or marked emotional instability, epilepsy, parkinsonism, and a history of blood dyscrasia be placed in "Contraindications" in the labeling, I have drawn the following conclusions as a result of discussions with the company:

Since patients with renal disease have received the drug without difficulty, and there is no real evidence that the drug per se adversely effects renal function, it is not necessary to put renal disease in "Contraindications".

Despite the experience of R. G. Robinson, emotional disturbances with Indomethacin have not been very common. Although here have been instances of aggravation of emotional disorders with indomethacin, the data are probably insufficient to make these a contraindication for drug use and a statement in "Warnings" would seem to cover the situation for the present. Similar considerations apply to epilepsy and parkinsonism.

I called Dr. Bernard Norcross on April 8, 1965, to inquire concerning his experience relative to CNS disturbances in his 500+ patients on indomethacin. He has not observed any psychotic reactions or aggravation of existing neuroses in his patients. Two patients with severe headache due to drug reported "peculiar" sensations.

With regard to contraindication in patients with a history of blood dyscrasia, I agreed with the company that there is no evidence indicating that indomethacin may cause blood dyscrasia in patients who have in the past developed a blood dyscrasia spontaneously or as the result of other drugs. It might behoove a physician to be cautious when he introduces a new drug to a patient with previous sensitivity to another drug, but this could apply to any new drug as well as to indomethacin.

MEMO OF INTERVIEW, APRIL 8, 1965—DR. JAMES SHAFFER, MERCK SHARP & DOHME, AND MARION J. FINKEL, M.D., MEB/DND/BM

SUMMARY OF SUBSTANCE OF CONTACT

Dr. Shaffer verbally reported that Dr. Norman Rothermich performed BUN, creatinine, inulin and PAH clearance studies on 7 patients who had been on indomethacin for 2½ to 3 years and found all levels within normal limits. Dr. Felix Demartini had done pre- and post-treatment studies in one patient on drug for 5 weeks and found no change. Dr. Bernard Norcross had done acute studies in 3 patients given 60 mg. indomethacin I.V. and found no changes. Dr. Shaffer inquired whether these studies would be sufficient or would we still require the 3 month renal studies before approval. I stated that the negative acute studies of Norcross shed little light on the problem, but Rothermich's studies may be of significance. However, the 3 month studies might reveal whether a downward trend was evident and would be helpful from that standpoint.

Dr. Shaffer indicated that Norcross has 1 patient on 3 month studies and that 3 other investigators have or will begin studies.

Dr. Shaffer is going to prepare the data on Rothermich's patients and will bring them in.

Dr. Shaffer agreed to move the sentence concerning possible aggravation by drug of emotional disorders, epilepsy and parkinsonism from "Precautions" to "Warnings" in the package circular.

MERCK SHARP & DOHME RESEARCH LABS.
West Point, Pa., April 13, 1965.

MEMORANDUM OF TELEPHONE CONVERSATION BETWEEN ARTHUR D. DAVIS, OFFICE OF ASSISTANT COMMISSIONER FOR PLANNING, AND HOWARD D. COHN, M.D., CHIEF, MEDICAL EVALUATION BRANCH, DND

Mr. Davis called to informed me that Representative Fogarty had contacted Commissioner Larrick relative to the above mentioned drug, particularly in regard to any problems with the application or potential approvability. I advised Mr. Davis that we are currently in the final stages of review of the application and had met with the firm on several occasions and are planning to meet again with them on April 22. I briefly outlined for Mr. Davis a description of the drug and its indications and contraindications. Mr. Davis asked for a memo on this immediately, and accordingly I wrote this and it was sent to him on the same day.

MEMORANDUM OF INTERVIEW BETWEEN DRS. DOUGLAS LAWRASON AND JAMES SHAFFER, MERCK SHARP & DOHME RESEARCH LABORATORIES, AND ARTHUR RUSKIN, M.D., DEPUTY DIRECTOR, DND, HOWARD D. COHN, M.D., CHIEF, MEDICAL EVALUATION BRANCH, DND, MARION J. FINKEL, M.D., MEDICAL EVALUATION BRANCH, DND

Representatives from Merck came in to present some additional data on renal clearance studies in patients on Indocin (indomethacin). Dr. Shaffer reviewed for us the experience on this subject. As far as the firm is concerned they do not feel there is any evidence of renal toxicity. Some additional subacute work (three-month study in South Carolina) is presently being performed. It may not be necessary to await this report if the present submission looks satisfactory after Dr. Finkel has had a chance to review it.

The second part of the discussion concerned the NDA for Triavil. Merck has contacted Schering; and Dr. Lawrason told us about his conversation with Dr. Augustus Gibson, who feels that the eighteen deaths with Etrafon (our records indicate seventeen deaths) are not drug related. In answer to his question as to what Merck could do next, the only answer we could give them was that we would have to await additional clarification on these deaths from the Schering people.

Memorandum to: Dr. J. F. Sadusk, Jr., Medical Director.
From: M. R. Stephens, Assistant Commissioner for Regulations.
Subject: NDA 16-059, Indocin Capsules.

We are in receipt of the proposed letter to approve Merck Sharp & Dohme's Indocin Capsules (NDA 16-059). Accompanying the file is a memorandum of June 4, 1965 from Dr. Marion J. Finkel in which she advises that the final printed labeling which has been submitted contains all of the Bureau of Medicine's recommendations and concludes that this drug is "safe" and effective for the indications in the labeling.

A review of this file shows that the initial comprehensive summary was made in December by Dr. Finkel and that based on this summary a letter of January 13, 1965 was written to Merck Sharp & Dohme regarding a number of questions about the application and ruling it incomplete. Since that time there have been a number of discussions by telephone and otherwise and some new submissions. We believe for this file to be adequate for approval of the new-drug application that we should have an up-to-date summary on this drug. We believe that the summary should, among other things, deal with all the questions raised in our letter of January 13, 1965, and any of the other intramural or intermural discussions. For example, your letter of January 13, 1965 among other things, raises the need for clinical studies on a number of conditions, including osteoarthritis of the hip and other locations. Also, Dr. Finkel's memoranda of telephone calls of February 12, 1965 and April 8, 1965 with Dr. James Sharp raise questions of the adequacy of the data in support of the claims for osteo-arthritis of the hip and also raise questions as to the adequacy of the data to negate any conclusion of renal damage arising out of the use of the drug. Perhaps the latter submissions of Merck Sharp & Dohme have answered all of these questions. If so, the up-to-date summary should reflect this.

M. R. STEPHENS.

NOTE.—The substance of this memorandum was furnished to Drs. Ruskin, Cohn and Finkel today. Dr. Finkel stated she will proceed to prepare a current summary of the medical facts and conclusions from all of her other memos in the file.

INTRA-ADMINISTRATIVE REFERRAL—AUGUST 25, 1966

REFERRALS AND RECOMMENDATIONS

MR. KIRK: This "anti-rheumatic" drug has been marketed under NDA approval for a little over a year. During this time the number and seriousness of adverse reactions and deaths has apparently resulted in the present 5 page letter having been written. The letter points out the label corrections needed. Among the numerous warnings, precautions, side effects, etc., is the requirement that following the name of the drug will appear: "Not Recommended for Use in Children".

In the material I have at hand (vol. #67 of the NDA and copies of memoranda and outgoing letters) I find reference to three deaths, in children, attributed to this drug. (There probably are others). I presume the warning against use in children stems from these deaths.

I, of course, have no figures as to how many children have been treated with the drug nor how many serious adverse reactions and deaths resulted. I presume the numbers have not been great. On the other hand, in the material here (vol. #67 and correspondence) I find references to 12 adult deaths connected with the use of the drug. (This does not include a 24 year old whose doctor managed to pull him through an "apparently impending death".) The ages of these adults were 23, 58, 59, 77, and 81. (Seven of the references did not list ages).

While apparently these rheumatic diseases do occur at just about any age, I believe the frequency is much higher at advanced ages. Nevertheless what is the rationale for the warning "Not recommended for use in children" when there may be as high of percentage of serious reactions with treated patients in other age brackets such as teenagers, 20–30 year olds, 30–40 year olds, etc.? Perhaps the drug should have restricted use at any age?

The letter refers to the revision of the package insert. What about the "direction circular" which goes to the physician?

Dr. Seife's Medical Summary of 7/15/66 points out that the opening paragraph statement "unlike corticosteroids, it has not effect on pituitary or adrenal function" is open to question. If such a positive statement is open to question shouldn't it be deleted?

In view of the reported cases of nosebleed and temperature elevation shouldn't these be listed as adverse reactions? (A temperature rise is of course paradoxical in view of the drug's anti-pyretic activity.)

In view of the reports of life threatening severe reactions (including at least one death) in asthmatics should this, perhaps, be a contraindication?

Perhaps my assumption that the drug is not recommended for children because of deaths and severe reactions is an incorrect one but if it is so, then last paragraph under "contraindications" is misleading since it gives the reason as limited experience. In any event the required statement "Not Recommended for Use In Children" seems contradictory to the requested bold face type statement ". . . should not be administered to pediatric age groups until the indications for use and dosage have been established". This could imply that the individual physician is to experiment with the drug on his pediatric patients to determine use and dosage on an individual basis.

Dr. Seife's 4/29/66 Evaluation of N.D.'s 1966 statements on Indocin states that it fails to mention that the drug is not likely to be effective in cases of severe rheumatoid arthritis. The same criticism can be made for the labeling of Indocin. On the other hand, should a toxic drug like Indocin be used for rheumatoid arthritis at all if its efficacy is only in mild or moderate cases. (Rheumatoid arthritis is the principal indication for use).

In the same report Dr. Seife states that a few fatalities have occurred and severe adverse effects, requiring discontinuance of the drug in many patients, are common. In fact, indomethacin is too hazardous to be substituted for aspirin when the drug (aspirin) is effective." Yet under "Indications" the insert states ". . . . indomethacin may often replace other commonly used agents such as corticosteroids, salicylates. . . ." There are other references to reducing or stopping salicylates which may imply that Indomethacin is a substitute.

RAYMOND E. NEWBERRY.

Senator NELSON. We will recess for 5 minutes, and then resume with Dr. Jennings.

(A short recess was taken.)

Senator NELSON. Dr. Jennings, we are pleased to have you here today. You did submit a biographical sketch which will be printed at this point.

(The biographical material follows:)

CURRICULUM VITAE: JOHN JENNINGS, M.D.

Date of Birth: 3/24/24, Passaic, New Jersey.

June 1949: M.D. College of Physicians and Surgeons, Columbia University, New York.

July 1949–June 1950: Rotating Internship, Jersey City Medical Center, Jersey City, New Jersey.

July 1950–Dec. 1950 and July 1952–Dec. 1954: Residency, Internal Medicine and Veterans Administration Hospital, Bronx, New York (36 months).

Jan. 1951–May 1952: Medical Officer, U.S. Army.

Jan. 1955–March 1958: Staff Physician, Veterans Administration Hospital, East Orange, New Jersey, (Medical Service).

June 1958–Oct. 1964: Private Practice, Internal Medicine, Clifton, New Jersey. Associate Attending, Medicine, St. Joseph Hospital, Paterson, New Jersey.

March 1959–Oct. 1961: (Part-time) Director, Medical Education, St. Joseph Hospital, Paterson, New Jersey. (Instructor: *Seton Hall College of Medicine and Dentistry*).

Oct. 1964–Nov. 1965: Medical Officer, Drug Surveillance Branch, Bureau of Medicine, Food and Drug Administration.

Nov. 1965–Mar. 1966: Acting Assistant Branch Chief, Drug Surveillance Branch, Bureau of Medicine.

Mar. 1966–July 1966: Acting Branch Chief, Drug Surveillance Branch, Bureau of Medicine.

July 1966–Nov. 1967: Acting Associate Director for Drug Surveillance, Bureau of Medicine.

Nov. 1967–Present: Acting Associate Director for Marketed Drugs, Bureau of Medicine.

Senator NELSON. Doctor, you may present your statement any way you see fit. I assume you have no objection to interruptions by questions.

STATEMENT OF DR. JOHN JENNINGS, ACTING DIRECTOR, OFFICE OF MARKETED DRUGS, BUREAU OF MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. EDWIN ORTIZ, DIRECTOR, DIVISION OF METABOLIC ENDOCRINE DRUG SURVEILLANCE, OFFICE OF MARKETED DRUGS, FDA; AND DR. DAVID HURWITZ, MEDICAL OFFICER, PUBLIC HEALTH SERVICE

Dr. JENNINGS. Not at all, sir.

Before I get to my statement, may I present two members of the staff, Dr. Edwin Ortiz, the Director of the Division of Metabolic and Endocrine Drug Surveillance, Office of Marketed Drugs, and Dr. David Hurwitz, who has been quoted earlier, who is a young Public Health Service medical officer assigned to the Food and Drug Administration.

The Office of Marketed Drugs, which I direct, is responsible for following the clinical and other experience with new drugs approved for marketing. The Office of Drug Surveillance was predecessor to OMD, which was formed in November 1967. I have been associated with this function under the different organizational structures for the past 3 years. Our primary responsibility is the continuing evaluation of all new safety and efficacy data, and proposed revised labeling in supplements for new drugs approved under the New Drug Application procedures. This is done primarily by maintaining constant surveillance over clinical experiences and reports of adverse reactions, including those submitted by any new drug applicant under the records and reports requirements of the Kefauver-Harris drug amendments. On the basis of such surveillance, OMD makes a determination whether there is a need for more restrictive prescribing information, additional side effects and contraindication information, withdrawal of the New Drug Application, or recall of the drug from the market.

Early pharmacologic studies with indomethacin had indicated an unprecedented potency when the drug was used to control inflammation in various animal models. It was hoped, at that time, that Indocin would have a high therapeutic ratio and thus offer a significant advantage over corticosteroids with their multiplicity of serious adverse reactions. Unfortunately, Indocin was shown to have a similar propensity to cause a wide variety of serious and sometimes fatal reactions, and its clinical usefulness has been limited by its toxicity.

The New Drug Application for Indocin was originally approved for use only in the following four conditions:

1. Rheumatoid arthritis;
2. Rheumatoid (ankylosing) spondylitis;
3. Degenerative joint disease (osteoarthritis) of the hip; and
4. Gout.

The manufacturer, in advertising and promotion to the medical profession, offered the drug as a new nonsteroid anti-inflammatory agent useful to extend the margin of safety in the long term management of arthritic disorders, and as the drug of choice in osteoarthritis of the hip and in gout. Since its introduction in 1965, Indocin has been widely accepted by the medical profession as an antiarthritic agent. During its first year on the market it became one of the 200 most-prescribed drugs.

We have received information from several sources that Indocin may be used beyond its approved indications, for such conditions as minor sprains, bursitis, trick knee, and so forth. It appears that some physicians may regard the drug as a general purpose analgesic, antipyretic anti-inflammatory agent. The 1966 promotion of the drug featured these effects. The promotion and advertising will be discussed later by Dr. Robert McCleery.

Senator NELSON. Do you have any comments to make on the comments of Mr. Kirk, the Acting Associate Commissioner for Compliance, in his letter of September 2, 1966:

> The Bureau of Medicine tells me this is a valuable drug, but that in their judgment it is being badly misused. It would seem this may be something like chloramphenicol as far as misuse is concerned, and perhaps this warrants a "Dear Doctor" letter.

Information is that it is one of the 200 most frequently prescribed drugs. Is it being widely overprescribed, in your judgment?

Dr. JENNINGS. I wouldn't be able to document that, sir. We have reason to believe that it is. That is, it has been, and probably still is being used for conditions other than those in the indications section of the label. But just how widely it is used for these conditions not listed we would have no way of knowing.

(The letter from Mr. Kirk follows:)

MEMORANDUM

To: James L. Goddard, M.D., Commissioner of Food and Drugs.
From: J. K. Kirk, Acting Associate Commissioner for Compliance.
Subject: Advertising and Labeling of Indocin, NDA 16-059.

While I am not too concerned about the labeling deficiencies pointed out by Mr. Newberry, I do believe this is a drug which warrants your personal consideration. You will note that it has been on the market for only about one year, has had many serious reactions (including about 15 deaths) and it is now proposed that we give the firm five additional pages of warnings, contraindications and adverse reactions which were not in the labeling when the drug was approved in 1965.

The Bureau of Medicine tells me this is a valuable drug, but that in their judgment it is being badly misused. It would seem this may be something like chloramphenicol as far as misuse is concerned, and perhaps this warrants a "Dear Doctor" letter.

The advertising feature which you will see in here was not pursued until we could get labeling, and there is a question as to whether we are in a position to proceed on the advertising feature when there is so much seriously wrong with the labeling.

I assume you will want to discuss this with Dr. Robinson after you have looked at the file.

J. K. KIRK.

Mr. GORDON. I have some information to the effect that in 1967 there were about 350 batches of this drug produced. There are 2 million capsules in each batch, I was told. That made a total, then, of 700 million capsules.

Does that sound like a lot of capsules?

Dr. JENNINGS. It sounds like a lot, yes.

I don't know the latest distribution figures for the drug offhand. I know that during the first 10 months that it went on the market there was something like 300 million capsules distributed.

I believe in the last period for which we have a record the amount did not decline, as a matter of fact, I think we have an 11-month period with something like 500 million capsules distributed. So the drug is very widely used.

Now, it would be extremely difficult for me to give you any hard and fast figures on how much of this use is outside of the approved indications. I think it is safe to assume that to this day such use continues.

Senator NELSON. You say 500 million capsules?

Dr. JENNINGS. Yes, sir. I would have to check on that.

Senator NELSON. The counsel says in 1967 his best information is that it was 700 million capsules. That is not too far off. What is the normal dosage? A capsule?

Dr. JENNINGS. Yes, sir; one dosage unit. And since the dosage ranges to 200 milligrams and the capsule is a 25-milligram capsule, I suppose you might derive some idea of how many patients there are at any one time.

But again I would be reluctant to hazard any hard and fast figure as to just how many patients other than those covered by the indications there might be at this time.

Senator NELSON. Do you know what the incidence of the disease are for which the drug is indicated?

Dr. JENNINGS. They are variously estimated to be as high as 5 million in this country. I couldn't give a good figure.

Mr. GORDON. It is not the drug of choice for rheumatoid arthritis, is it?

Dr. JENNINGS. No, sir.

Mr. GORDON. Isn't aspirin the first choice?

Dr. JENNINGS. Yes, accepting that term in the sense that you mean it, I would say aspirin is the first drug that should be tried in chronic rheumatoid arthritis.

Mr. GORDON. And can you assume that it would be used only when a patient cannot take aspirin?

Dr. JENNINGS. Or when a patient perhaps failed to benefit from those dosages of aspirin which would ordinarily give relief or which would give the minor side effects, which would be used to gage the maximum tolerable dosage of aspirin.

Mr. GORDON. Were those many in number?

Dr. JENNINGS. I figure that they constitute probably a significant number of chronic rheumatoid arthritis patients. I wouldn't begin to estimate how many.

Mr. GORDON. What I mean is, how many of those who take Indocin for rheumatoid arthritis are taking it because aspirin doesn't do them any good? How many people take aspirin and don't benefit from it and have to take Indocin?

Dr. JENNINGS. I can't answer that exactly. The drug is not restricted in its use at the current time to those who are unable to take aspirin or who have not benefited from aspirin. I think, however, that the labeling overall would lead the conscientious practitioner to a course of this nature, that is, if a patient taking an amount of aspirin that ordinarily provides relief fails to get relief, he might consider using Indocin.

On the other hand, it may be that a doctor might try Indocin in a patient who was obtaining some relief, perhaps not optimal relief, and who was perhaps having some of the side effects associated with aspirin. Many patients with chronic rheumatoid arthritis eventually end up on a regime of more than one drug, the combination of aspirin and steroids being not unusual.

It became apparent after approval of Indocin that the drug was causing frequent adverse reactions. For the most part, the adverse reactions reported were those which were mentioned in the labeling originally approved for the drug. However, with the passage of time, other reactions, occurring somewhat less frequently, were reported.

Among the adverse reactions reported to us by July 1966, were five deaths in children being given this drug. Let me say that the labeling for Indocin, since its initial approval for marketing, has listed under the heading of "Contraindications" the recommendation that the drug not be administered to pediatric age groups. A major problem here, in addition to the known adverse effects on adults, is that the drug, like other anti-inflammatory agents, may mask the symptoms of infections by suppressing the inflammatory process, allowing the infection to spread unchecked.

At the present time, we have received reports of a total of 14 deaths of children being treated with Indocin, both foreign and United States. The age range of these children was 4½ months to 14 years. The reported causes of death are as follows.

And I have listed the reported causes of death and the judgment made by us from the data we have as to whether Indocin was possibly or likely related to the cause of death. I want to go through that very briefly.

(The table follows:)

	Cause/effect		Total
	Possible	Unlikely	
Hepatitis	3		3
Peptic ulcer with perforation	2		2
Peptic ulcer with hemorrhage	1		1
Infection	2		2
Sudden death (infants already severely ill)		2	2
Pneumonitis with alveolar cell proliferation		1	1
Severe enterocolitis	1		1
Rheumatoic myocarditis with sinus thrombosis		1	1
Renal failure		1	1
Total	9	5	

Dr. JENNINGS. Hepatitis, three cases, in all three of which we thought Indocin was a possible cause.

Peptic ulcer with perforation, two cases, in both of which we thought Indocin was a possible cause.

Peptic ulcer with hemorrhage, one case, in which we thought Indocin was a possible cause.

Infection, two cases, in both of which we thought Indocin was a possible cause.

Sudden death (infants already severely ill), two cases, in both of which we thought it was unlikely that Indocin was the cause.

Pneumonitis with alveolar cell proliferation, one case, and we thought it was unlikely that Indocin was the cause.

Severe enterocolitis, one case, in which we thought it was possible that Indocin was the cause.

Rheumatoid myocarditis with saggital sinus thrombosis, one case, in which we thought it was unlikely that Indocin was the cause.

And renal failure, one case, in which we thought it was unlikely that Indocin was the cause.

So of the 14, nine were possibly and/or probably related to Indocin, and five were unlikely.

Indocin was not considered to be the cause of death in all of these cases. A number of these children were severely ill and in all likelihood died from the effects of their primary diseases. Others were on other potent concomitant therapy, which may have contributed to their death. However, some of the deaths may well have been caused by Indocin.

On July 15, 1966, members of the Bureau of Medicine met with representatives of Merck Sharp & Dohme at our request to review the adverse clinical experience with the drug. At this meeting, the firm was requested to revise its package insert to reflect the new clinical experience. FDA requested that the labeling include additional warnings, contraindications, adverse reactions, and precautions. Incidentally, by regulation, these changes could and should have been put into effect by the firm at the earliest possible time, without awaiting approval from the FDA.

In the light of the additional data involving the five deaths in children, we requested that the warning against its use in children be placed in bold type at the beginning of the package insert. In addition, it was recommended that the labeling carry a warning statement, also in boldface type, to the effect that Indocin is not an innocuous drug and should not be used in conditions other than those recommended under "indications."

Mr. GORDON. May I ask you a question at this point? Why do you say "is not an innocuous drug"? Why can't you just say "dangerous drug"? Are you not really using a euphemism?

Dr. JENNINGS. I suppose so.

Mr. GORDON. You are saying that this is a dangerous drug; isn't that correct?

Dr. JENNINGS. Yes, sir, I guess we could say that about almost any drug.

Mr. GORDON. We are talking about this drug as a dangerous drug. Why do we have to use this "innocuous" euphemism?

Dr. JENNINGS. I don't suppose we have to. I don't think that the meaning is vastly different, except that we hate to label the drug as dangerous when it is going to be given to people who are aware what they are taking.

Anyone who has a chronic disease knows in a very short time not only what drug he is taking but how many milligrams of it he is taking. And it seems to me that to label a drug that is going to be administered to a large number of people as a dangerous drug would serve no useful purpose. The drug is dangerous, as are many other potent drugs, in that it can cause severe side effects. It is not dangerous when properly used for its proper indications and with the precautions listed in the labelings.

Mr. GORDON. Isn't it dangerous even though it is used for its proper indications?

Dr. JENNINGS. Yes, sir, it has an inherent danger. And that is why the labeling is so replete with precautions and counterindications, and warnings.

Mr. GORDON. Now, here is something that puzzles me. You say that: "By regulations these changes can and should be put in effect at the earliest possible time without awaiting approval by the FDA."

Dr. JENNINGS. Yes, sir.

Mr. GORDON. However, on September 2 of the year 1966 you were still arguing with the company about how you were going to record these adverse side effects; is that correct?

Dr. JENNINGS. Essentially.

Mr. GORDON. And so from April you knew, or at least the firm knew, about these side effects?

Dr. JENNINGS. Well, we met with them in July, after having gathered together our information, and having decided what additional information we thought should be in the labeling.

Mr. GORDON. You met in July, you met in September, but you knew about the many adverse side effects in April?

Dr. JENNINGS. We knew about many side effects before the drug was approved. We began to monitor the reports as soon as the drug was on the market. But we don't as a rule require immediate labeling changes every time that we have a new or possible adverse reaction. It just wouldn't be practical from a number of points of view for us to attempt to require that the firm revise its labeling every time we have some new bit of information. We don't have the personnel and the machinery for bringing about such changes.

Mr. GORDON. You admit that from July, or certainly from July to September, maybe later, the doctor was uninformed about these new changes that were taking place; is that correct?

Dr. JENNINGS. Yes, sir.

Mr. GORDON. And they were important changes, too, I presume, since you were insisting on them.

Dr. JENNINGS. Yes; they were important in the sense that they reaffirmed and pointed up some of the previously mentioned warnings, precautionary material, and side effects.

There actually was nothing new, you might say, in these changes other than the addition of some side effects which had become apparent in the postmarketing period. The warning against the use in children admittedly was not perhaps as prominent as it might have been but it certainly was in the warnings under the heading "Contraindications."

Mr. GORDON. My point is that there were several months during which the doctor was not aware about this new information.

Dr. JENNINGS. There were several months during which the packaging insert was in process of being revised; yes, sir.

Mr. GORDON. And the firm could have done all this without approval from you under section 130.9 of the regulations; is that right?

Dr. JENNINGS. Yes, sir.

Mr. GORDON. And they didn't do it?

Dr. JENNINGS. No, sir.

Mr. GOODRICH. They did in October.

Dr. JENNINGS. Yes.

On September 2, 1966, we received the new revised labeling from the company. It contained all of the changes recommended at the July meeting except (1) our recommendation for the bold-type opening pediatric warning statement, and (2) the warning that Indocin is not an innocuous drug and should be used only in conditions for which it was approved.

Rather than wait for all the recommended labeling changes to be worked out with us, interim revisions of the labeling were put into effect by the company without our advance approval. The revisions were:

The drug was contraindicated in "aspirin-sensitive asthmatics."

The following paragraph on precautions was added:

> In common with other drugs which have anti-inflammatory analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. Indomethacin should be used with caution in patients with existing, but controlled infections.

Lastly, the labeling included information about new adverse reactions noted with the use of the drug, as follows: Convulsions, jaundice, hepatitis, elevation of blood pressure, angitis, hematuria, alopecia, acute respiratory distress including sudden dyspnea and asthma, leukopenia, purpura, thrombocytopenia, agranulocytosis, orbital and periorbital pain, vaginal bleeding, hyperglycemia, and glycosuria.

In early October 1966, the drug's sponsor sent a "Dear Doctor" letter to all physicians advising them of these labeling revisions. The letter was not cleared with us. Review of the letter after it had been circulated indicated that the firm had worded the message in such a way so as to turn it into promotional literature for the drug. Thus, the original intent of the letter to warn the physicians of the drug's additional hazards was completely lost. I am submitting a copy of this "Dear Doctor" letter for the record.

(The letter follows:)

MERCK SHARP & DOHME,
DIVISION OF MERCK & CO., INC.,
West Point, Pa., October, 1966.

DEAR DOCTOR: It is only natural that with over 144,000,000 patient days of therapy in 99 countries, we have added to our cumulative knowledge of INDOCIN® (Indomethacin) in the treatment of arthritic disorders. This greater experience is reflected in the revisions contained in the enclosed package circular. These revisions will be made in all promotional material and package inserts as rapidly as possible.

While we urge you to acquaint yourself with the entire package circular as revised we want to call your attention to one change in particular:

"In common with other drugs which have anti-inflammatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. Indomethacin should be used with caution in patients with existing, but controlled, infections."

This and other important changes in the package circular have been set in boldface type so that you may find them easily. They should assist you in the more effective use of INDOCIN—which has become, next to aspirin, the most frequently prescribed antirheumatic drug.

Sincerely yours,

FREDERICK K. HEATH, M.D.,
Vice President, Professional Communications.

Dr. JENNINGS. Shortly after mailing this "Dear Doctor" letter, and partly as a result of our public criticism of the advertising of the drug, the firm was invited to meet with Dr. James L. Goddard, Commissioner of Food and Drugs. At this meeting, the firm agreed to revise its labeling by placing at the beginning of the text of the package insert, in bold type, the following statement:

> Important Note: Indocin (Indomethacin) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under indications. The drug should not be prescribed for children because safe conditions for use have not been established.

At the same time, the firm agreed to issue a second "Dear Doctor" letter [1] including the new revised package insert with its strengthened warnings. The text of this letter, under the letterhead of Merck Sharp & Dohme, read as follows:

> DEAR DOCTOR: From time to time, we have sent you new information regarding "Indocin" (indomethacin) as greater clinical experience is gained. At this time, I would like to reiterate that the drug should be used only in those conditions which are indicated in the package circular and it should not be prescribed for children because safe conditions for use have not been established.
>
> We are reminding the physician of this by placing an important note to this effect at the beginning of the package circular, a copy of which is enclosed. There are a few other changes in the circular and for easy recognition these have been put in bold-face print.

Since approval of the original NDA, the firm has submitted two supplements to provide for additional indications for use of the drug.

On December 10, 1965, the firm submitted a supplement for its use in dental surgery. On May 23, 1966, the firm submitted a second supplement to provide for use of the drug in the treatment of osteoarthritis and acute musculoskeletal disorders. (These two indications were proposed in the original NDA, but were not approved.) It was concluded that the proposed new indications were not supported by adequate data and neither supplement was approved.

Senator NELSON. I thought that the FDA had to approve the labeling.

Dr. JENNINGS. Yes, sir; that is essentially true. There is a provision, however, under the section mentioned by Mr. Gordon, 130.9, which permits the company to add certain types of material to its package inserts, labeling, without prior approval; anything that goes to warnings, contraindications, or precautionary terms.

But at no time are they allowed to add new indications that would expand the use of the drug. And even the changes that they are permitted to make without approval are subject to later approval by us.

Senator NELSON. Now you state that they accepted all the changes recommended in July, except the pediatric warning statement?

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[1] Full text of second letter and enclosure begin at p. 2994, infra.

Dr. JENNINGS. Yes.

Senator NELSON. Then, as I understand it, they did include this warning, and then sent out the package label?

Dr. JENNINGS. That is right.

Senator NELSON. So despite the fact that you had recommended all the changes in July, they went ahead and omitted two significant recommendations without coming to the agency for approval, and sent out the package insert?

Dr. JENNINGS. That is right.

Senator NELSON. And then what did FDA do?

Dr. JENNINGS. We didn't accept that. This happens frequently, with labeling changes made under this section 130.9. And our usual procedure is to review the changes, and if we feel they are not adequate, we will inform the company that we think that further changes are to be made. And this is essentially what happened. It is getting a little ahead of the story here, but that is essentially what took place in this case.

Senator NELSON. In order to have it all in one place in the record, how soon after they sent out the unapproved labeling were the corrections made?

Dr. JENNINGS. It was in early October that they send out their "Dear Doctor" letter, which included the revised labeling with the omissions that we noted. And it was shortly thereafter that they were invited to meet with Dr. Goddard. And it was following that meeting that the labeling was revised further to our satisfaction.

Mr. GROSSMAN. Doctor, at this point I would like to ask you, I think Dr. Hodges mentioned this. I notice the company sent out a "Dear Doctor" letter, and then another "Dear Doctor" letter. How many doctors are going to start looking——

Dr. JENNINGS. I think that is a real problem, and one that has concerned us considerably in the Bureau of Medicine. I don't think that applies in this case, because the changes here would signify——

Mr. GROSSMAN. You are well aware of how much mail these doctors receive on promotional material, and so forth.

Dr. JENNINGS. Yes.

Mr. GROSSMAN. If you start using these "Dear Doctor" letters for every little thing, they are going to lose that much faith in them.

Dr. JENNINGS. That is right. And that is why we must use this method of communicating with the doctors only on important items.

Mr. GROSSMAN. And yet this letter went out without the approval of the FDA.

Dr. JENNINGS. That comes under the heading, we feel, of "promotional literature." And we have no way that I know of, of restricting it.

Mr. GROSSMAN. Did it go out as a "Dear Doctor" letter—is there a difference between the "Dear Doctor" letter——

Dr. JENNINGS. There is no official status of a "Dear Doctor" letter.

Mr. GROSSMAN. It looks exactly the same to the doctor, then?

Dr. JENNINGS. The letter that is sent out by the company on its own, which may be promotional, has no special characteristics. One that is sent out by the company at the request, urging of the Food and Drug Administration, must satisfy certain criteria.

Mr. GROSSMAN. It does satisfy something on the envelope?

Dr. JENNINGS. Yes, sir.

Mr. GROSSMAN. So the second matter that was sent out did have something on the envelope?

Dr. JENNINGS. These regulations hadn't been established at that time, but it was marked. I have copies of that letter.

Mr. GROSSMAN. So in essence the two letters looked the same?

Dr. JENNINGS. Yes, they did, quite a bit, on the outside.

Mr. GROSSMAN. And the doctor would have no way of knowing that you didn't approve the first one?

Dr. JENNINGS. No, he wouldn't at that time, and he wouldn't today.

Mr. GROSSMAN. Under your new regulations would he?

Dr. JENNINGS. I believe he would. They are quite clearly marked.

Mr. GROSSMAN. Would he or would he not?

Dr. JENNINGS. I don't know, however.

The envelope is clearly marked with a standard set of markings today.

Mr. GORDON. Doctor, on the envelope it merely says, "Drug Safety Information." Do you think that that is strong enough?

Dr. JENNINGS. No, sir. And that is one of the reasons we now have a system of standard markings for the exterior of the envelope which tells the doctor the sort of information that is contained inside.

Mr. GORDON. This second letter was designed to undo what the first letter was supposed to have done; is that right?

Dr. JENNINGS. To a certain extent.

Mr. GORDON. Actually it was a remedial letter. I have it here in front of me. It seems to be rather weak. Is this sufficiently strong to undo the damage done by the very first letter?

Dr. JENNINGS. That is a difficult question to answer. I would say that today it probably would not read exactly as it did then, just as an envelope would not be marked as it was then.

Mr. GORDON. There is nothing to indicate that the FDA required the firm to send out this letter.

Dr. JENNINGS. No; that isn't in the letter.

Mr. GORDON. But that is an important point, don't you think?

Dr. JENNINGS. I think it can be an important point under certain circumstances. I think, however, in a fair balance here, that the letter does point out the important passages of the new package insert certainly, and effectively reminds the physician that the drug has certain indications, and that it should be used only for those.

Senator NELSON. The first letter sent out was—obviously was from the FDA standpoint, an inadequate letter; is that not correct?

Dr. JENNINGS. Yes, sir.

Senator NELSON. A doctor reads that first letter, and he is busy, and then he sees another one, and it contains further explanations. The reason you required the firm to send the second letter was that the first one was misleading and gave bad information. Why shouldn't you require the company to say, "We sent you a letter on such and such a date, and the FDA has required us to send you another one clarifying this situation"? Why shouldn't you just bluntly make them state to the doctor, "We misled you," in effect, so that physicians will realize that they have been relying on misinformation? Why do you have to be so soft on the company, particularly when they sent the package label out without accepting the recommendations you had suggested?

Dr. JENNINGS. Well, I am answering after the fact, and it is a luxury I don't usually enjoy. So I can say that I agree that it probably should have been more pointed in that regard. I did not personally have approval of this letter, and I cannot say that under the circumstances that prevailed at that time I would have taken the tack that you so correctly indicate today. I think I can assure you, however, that were something of this sort to happen again, the points that were made by several members certainly would be carried out.

The matter of the marking of the envelope, and the fact that this letter was sent out at the request of the Food and Drug Administration, and probably a direct quote of the pertinent parts of the package insert in the body of the letter, all this would be included, I think, today.

Senator NELSON. And you say that that is going to be the policy of the FDA?

Dr. JENNINGS. Yes, sir.

Senator NELSON. And they will have to refer to the fact that they have been required to send the explanatory material?

Dr. JENNINGS. I think a review of the recent so-called remedial letters points this up; it is usually noted quite prominently that the letter is sent out by request of the FDA, and it usually requires that the important change be incorporated in the body of the letter so that the doctor has at least that opportunity to read it.

Mr. GORDON. Why did the Merck Co. refuse to strengthen its language?

Dr. JENNINGS. I think they were of the opinion that the contraindication was a strong warning in itself, and it was only when we confronted them, as it were, with the fact that the reason for the contraindication had changed that they were agreeable to making that change.

Mr. GORDON. I would like to read to you from a memorandum from the Acting Director, Division of Medical Advertising, Dr. McCleery, to Dr. Ley, dated November 2, 1966, in which he says:

> Their unwillingness to state "Not for use in children" appears irresponsible in the face of their knowledge of deaths in children—deaths not prevented by the old FPL language they even here aver to be inadequate.

Do you feel that their warning was adequate?

Dr. JENNINGS. I think that as Dr. Hodges indicated earlier in the day, it was considered adequate at the time that it was approved with the original approval of the drug. No, we didn't consider it adequate as things developed. And of course we did request a strengthening of that warning.

Mr. GORDON. They certainly resisted any change; did they not?

Dr. JENNINGS. Yes; I think you can say that they resisted it.

In the first quarter of 1967, major scientific and medical journals published new studies which disputed the usefulness of Indocin in rheumatoid arthritis. One of the most significant reports was a clinical study carried out by the Cooperating Clinics Committee of the American Rheumatism Association, in association with Dr. Donald Mainland. In this study, Indocin was compared with a placebo on 141 patients. The authors were unable to find any statistically significant difference between Indocin and the placebo.

In the same month—January 1967—Donnelly et al. published a similar study—30 patients—in the British Medical Journal. These authors used a double-blind crossover study comparing Indocin with a placebo. They, too, were unable to establish any statistically significant difference between Indocin and the placebo.

In a third article by Pinals and Frank, no difference was found between Indocin and aspirin in the treatment of rheumatoid arthritis. This study was a double-blind crossover type involving 24 patients.

Another article, by Pitkeathly, Banerjee, Harris, and Sharp, which appeared in the July 1966 Annals of the Rheumatic Diseases, reported a crossover trial of Indocin and soluble aspirin. It was concluded that Indocin should not replace aspirin in the routine treatment of inpatients with rheumatoid arthritis—but that some patients appeared to do better with Indocin and that it was useful in selected cases.

Mr. GORDON. Doctor, would you say that "selected" here means relatively few cases?

Dr. JENNINGS. I don't think that "selected" refers to the number, but rather to the type.

Mr. GORDON. Are occurrences of this type relatively few in number?

Dr. JENNINGS. Compared to the great mass of rheumatoid arthritics, probably yes, sir.

These studies, which we can accept as adequate and well controlled in spite of certain shortcomings, which are almost impossible to eliminate, show that under the test conditions Indocin has little or no statistical advantage over aspirin or placebo. However, it should be noted that statistical studies do not always reveal the benefit to the patient who is helped by the test drug and not by the control. The patients in these four studies were select groups; they were for the most part able to take aspirin and benefited from taking it.

In summary, these later studies, taken together with the data previously reviewed and discussed here by Dr. Hodges, serve to better delineate the place of the drug in the armamentarium of the treatment of rheumatoid arthritis.

We have under review a revision of the labeling for this drug to include certain newly reported adverse reactions. We intend to revise the indications section of the labeling to more accurately reflect the exact place of Indocin in the treatment of rheumatoid arthritis.

I am submitting for the record a tabulation of the adverse reactions, and capsule case histories of the deaths in children, that have been reported to us since Indocin's introduction in June 1965.

We have never regarded Indocin as an innocuous drug. We recognized from its very inception that the drug was capable of causing a wide variety of adverse reactions. The labeling, under which the drug was originally approved, reflected our knowledge of the reactions which were then known to be associated with its use. We know from experience that only after a drug has been extensively used over a long period of time by the medical profession at large can we fully assess its safety and effectiveness. As new reactions were reported through our surveillance operation, we required revision of the labeling to reflect these new adverse reactions or precautions. In addition, when it became apparent that physicians were not always heeding the cautionary statements in the labeling, we required the firm to place a strong warning statement at the beginning of the drug's labeling and to mail a "Dear Doctor" letter advising the profession of the hazards and proper indications for the drug. Thank you.

Senator NELSON. In the light of the controlled studies that you mentioned, what would you say is the place of Indocin in the treatment of rheumatoid arthritis?

Dr. JENNINGS. I would say it is efficacious for a number of patients with rheumatoid arthritis, some of whom may not have benefited by aspirin taken in dosage usually conferring benefit, or who might not be able to take adequate dosage of aspirin.

I will go further to say that in view of what you might term the qualitative difference in the adverse reactions reported with Indocin and aspirin, that it probably should not be used to initiate therapy in chronic rheumatoid arthritis.

Mr. GORDON. On page 11 you say you know from experience that only after a drug has been extensively used over a long period of time by the medical profession at large can we fully assess its safety and effectiveness. Wouldn't early and careful studies similar to the ones you just mentioned——

Dr. JENNINGS. No, sir; it is very obvious that these studies referred to didn't indeed turn up adverse reactions. In these studies Indocin came out just about like aspirin as far as adverse reactions were concerned. So obviously this isn't the type of study which gives the necessary type of information on reactions to drugs.

Senator NELSON. What is your viewpoint about establishing some further method of testing drugs for efficacy in addition to the testing financed by the companies; that is, some method similar to the American Rheumatism Association Cooperating Clinics Committee study?

Dr. JENNINGS. I think, as Dr. Hodges indicated, that it is a consummation devoutly to be wished, in spite of the many obstacles to establishing such an institute. I think it would be tremendously difficult and terribly expensive, but it probably could be done.

Senator NELSON. What do you visualize as the difficulties?

Dr. JENNINGS. Well, first of all, the clinical trial of drugs is something that, as we have recognized here, requires certain training and expertise. It is only recently, I believe, that NIH and some of the other Government agencies have indicated an interest in this type of research.

The Kefauver-Harris amendments created a need for this type of study. People came forward to provide a service to fill that need. And we know that some of them are quite competent and conscientious, and others are not. But in any event, they are essentially providing the service for a fee. And I think it would be a good thing if some neutral party, financed perhaps by the drug firms, but removed from their control and influence, were to be able to monitor and even design the studies.

We would still be confronted with the fact that there are very few people that are both competent and willing to engage in this kind of research. We would still have the difficulty of finding adequate numbers of patients who will be suitable for research purposes.

And you have to realize that they will be dealing not with animals that are bred for research and have become standardized so that one is almost identical to another, but with people who vary all over the place and who cannot be conveniently gathered together geographically. As an example in the ARA cooperating clinic study people were studied in various places by a multitude of investigators. Dr. Finkel, I think, indicated that there was one investigator for each 3½ patients. And that is not a good thing.

So it would be extremely difficult, but I don't think it would be impossible. And I think that something along this line deserves consideration.

Senator NELSON. Would any of your associates like to add anything?

(No response.)

Senator NELSON. I thank you very much for your valuable testimony. We appreciate your taking the time to come here today.

We will meet tomorrow at 10 o'clock in the caucus room.

(The supplemental information submitted by Dr. Jennings follows:)

INDOCIN—RÉSUMÉ OF DEATHS IN CHILDREN

1. A seven year old female with dermatomyositis was given Indocin, 100 mgm a day, for 10 months. She developed a pneumonia-like illness and succumbed. At autopsy, a peculiar alveolar cell proliferation was found. The diagnosis and cause of death is obscure. No definite relation to Indocin can be postulated.

2. An eight year old female with juvenile rheumatoid arthritis on 50 mgm of Indocin per day for 3 weeks developed a cholestatic hepatitis and died. Indocin was most likely the cause.

3. A six year old male on 180 mg per day of Indocin for 9 months developed a severe diarrhea and died. The presumptive diagnosis of enterocolitis was not substantiated at post. The cause of death is obscure. Indocin is a possible cause.

4. A nine year old female on 75–100 mgm daily intermittently during a one year period developed parotid swelling while on the drug. She died shortly thereafter. Autopsy showed that death was due to sepsis caused by B-hemolytic streptococci. Indocin may well have played a role in allowing the organism to disseminate without major symptoms until shortly before death.

5. An eleven or twelve year old male on 100 mgm of Indocin daily for an undisclosed period of time developed jaundice and gastrointestinal bleeding followed by death. Autopsy showed toxic hepatitis. Indocin is probably cause of this reaction.

6. A five year old male on 100 mgm Indocin daily for 4 days for rheumatoid arthritis developed CNS toxicity including emesis, irritability, tachypnea, hyperpnea, mydriasis and convulsions followed by alkalosis, GI bleeding and renal shutdown. The patient was on a fairly large dosage of aspirin and this drug may have been the cause of death since many of this child's symptoms were the same as those seen in aspirin overdosage.

7. An eleven year old male on 75 mgm of Indocin a day for 8 days developed laryngotracheitis and expired. Indocin was possible a cause.

8. An eight year old female developed a fatal toxic hepatitis after a one month course of Indocin, 50 mg/day.

9. A ten year old female with juvenile rheumatoid arthritis developed a peptic ulcer which needed surgery. Post operative complications, including peritonitis, lead to death. Although Indocin can cause ulcers, the patient was on steroids which are also ulcerogenic.

10. A fourteen year old male with rheumatic fever on 150 mg of Indocin per day for one month died of rheumatic myocarditis and sagittal sinus thrombosis. Indocin probably played no role in this death.

11. A nine year old female with rheumatoid arthritis died of a perforated ulcer. She was also taking salicylate and steroids, which are both ulcerogenic. Indocin possibly was contributory.

12. A twelve year old female taking Indocin, 100–125 mgm a day for 6 months to treat rheumatoid arthritis developed a fatal bleeding peptic ulcer. She was on steroids and salicylates. Indocin possibly was contributory.

13. A ten month old female infant severely ill with gastroenteritis died after a single dose of Indocin administered to control fever. Indocin probably played no role in the patient's death.

14. A 4½ month old male severely ill with pneumonia died after administration of a single dose of Indocin given to reduce fever. Indocin probably did not cause death.

MERCK SHARP & DOHME,
Philadelphia, Pa., September 23, 1966.

Re Indocin (indomethacin)—NDA 16–059.

OFFICE OF DIRECTOR,
Acting Associate Director Drug Surveillance:

This represents the position of the Office of Drug Surveillance regarding the various memos and letters relating to this drug currently circulating in the Bureau of Medicine.

1. It is generally recognized that Indocin is a potent drug with well recognized side effects which may be severe and occasionally fatal.

2. The original labeling, for Indocin was adequate in the light of the then current knowledge of the drug and its side effects. Indications for the drug were restricted to just four conditions. There were contraindications to use in children and in pregnancy. Warnings, Precautions, and Adverse Reactions' sections reflected the then current knowledge.

3. Since the original approval date, the drug has received extensive use.

Months	Number of bottles	Capsules (25 mg.)	Total capsules
July 1, 1965 to Sept. 30, 1965	693,900	100	69,393,000
Oct. 1, 1965 to Dec. 31, 1965	901,000	100	90,100,000
Jan. 1, 1966 to Apr. 30, 1966	1,459,000	100	145,800,000
Total, 10 months	3,053,900	300	305,293,000

As it became apparent that adverse reactions were frequent and occasionally severe, they were carefully monitored and tabulated. Although, in the main these consisted of those reactions which were mentioned in the original package insert, with the passage of time it became apparent that other reactions, occurring somewhat less commonly, were to be added to the original list. These will be discussed below. A number of deaths were reported associated with the use of the drug. The majority of these occurred in patients with rather severe rheumatoid disease frequently complicated by the presence of other conditions. However, there were five deaths in children which represented an abuse of the drug since such use was contraindicated in the original labeling.

4. On July 15, 1965 a conference was held between representatives of Merck Sharp & Dohme and the Bureau of Medicine. Revision of the labeling was requested at that time and, as a result of the conference, revised labeling was subsequently submitted under section 130.9. (A letter to the firm, detailing our requests for revision of labeling, was written but never sent. This letter included some requests which went beyond the usual requirements for labeling as well as some which were based on a limited number of cases without an established causal relationship. It did not request "five additional pages of Warnings, Contraindications, and Adverse Reactions which were not in the labeling when the drug was approved in 1965.")

This revised labeling submitted September 2, 1966 has been reviewed in the Division of Supplement Review. It contains all of the important changes suggested in the above conference and detailed in the resulting unsent letter, except for the following:

(*a*) A request to the pharmacist to place a special label on the dispensed package reading: "WARNING: Do not exceed recommended dose. Keep out of reach of children."

(*b*) An opening paragraph stating that Indocin is not an innocuous drug and that the cautionary statements in the labeling should be observed carefully.

The firm's objections to these changes are not without substance. However, DSR has recommended that some sort of cautionary opening paragraph be included in the labeling. This is not without precedent as the labeling for Butazolidin, a comparable medication, carries such an opening paragraph. The important point here is that the labeling for this drug was considered adequate at the time of approval and, as a result of updating as described above, is currently considered adequate with the minor exception of the opening paragraph.

5. Revisions of the labeling, which have been put into effect under 130.9, are listed below:

Contraindication

"Aspirin-sensitive asthmatics."

Warnings

No change.

Precautions

Possible "activation of latent infection" was requested. The paragraph included in the proposed labeling is as follows: "In common with other drugs which have anti-inflamatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. Indomethacin should be used with caution in patients with existing, but controlled, infections."

Adverse reactions

1. convulsions
2. jaundice
3. hepatitis
4. elevation of blood pressure
5. thrombophlebitis
6. angitis
7. hematuria
8. alopecia
9. acute respiratory distress including sudden dyspnea and asthma
10. leukopenia
11. purpura
12. thrombocytopenia
13. agranulocytosis
14. orbital and periorbital pain
15. vaginal bleeding
16. hyperglycemia
17. glycosuria

6. The Office of Drug Surveillance indorses Dr. Robinson's memo of July 19, 1966 regarding the proposed action against the firm concerning Journal advertising. The action is based on the then current labeling and it would appear that the JAMA advertisement cited is violative in several respects. Any changes in the labeling would not effect that interpretation, and in any event are in the direction of further restriction as pointed out above and would therefore strengthen rather than weaken the FDA case. A particularly strong case can be made on the basis of the omissions in the brief summary in the advertisement. The Office of Drug Surveillance strongly recommends that this action be pursued as probably the best possible way of correcting the violation and, at the same time, forcefully drawing attention of the Medical community to the restrictions in the use of this drug and the cautionary statements in the labeling.

7. The "Dear Doctor" letter. Except for the additional contra-indication, the changes in labeling are not of the sort that have usually prompted a "Dear Doctor" letter. *However, because there has been some abuse of the drugs which has in at least five cases resulted in the death of children, and because the drug has been misrepresented both in the lay and medical literature, a letter directing* the private physician's attention to, and reaffirming, the approved labeling might be in order. The effect of such a letter on the proposed action against the firm regarding its advertising should be considered. It is the position of the Office of Drug Surveillance that if the issuance of a "Dear Doctor" letter would in any way weaken the Administrations advertising case, or be considered as a substitute therefor, the letter should not issue. A successful action against the first on the basis of its promotion both in the lay and medical literatures would, with its attendant publicity, accomplish more immediately, and have a more lasting effect.

JOHN J. JENNINGS, M.D

MERCK SHARP & DOHME,
West Point, Pa., December 20, 1966.

DRUG SAFETY INFORMATION

DEAR DOCTOR: From time to time, we have sent you new information regarding 'Indocin' (indomethacin) as greater clinical experience is gained. At this time, I would like to reiterate that the drug should be used only in those conditions which are indicated in the package circular and it should not be prescribed for children because safe conditions for use have not been established.

We are reminding the physician of this by placing an important note to this effect at the beginning of the package circular, a copy of which is enclosed. There are a few other changes in the circular and for easy recognition these have been put in boldface print.

Sincerely yours,

FREDERICK K. HEATH, M.D.

CAPSULES—INDOCIN (INDOMETHACIN)—MERCK SHARP & DOHME

IMPORTANT NOTE.—Indocin (indomethacin) cannot be considered a simple analgesic and should not be used in conditions other than those recommended under "Indications." The drug should not be prescribed for children because safe conditions for use have not been established.

Indocin[1] (indomethacin) is a new drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds, and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

This drug is an effective anti-inflammatory agent that is suitable for long term as well as short term use in adult patients. It has been found effective to relieve pain; reduce fever, swelling, and tenderness; and increase mobility in patients with rheumatic disorders of the types listed.

INDICATIONS

Indocin (indomethacin) has been found effective in the symptomatic treatment of:

Rheumatoid arthritis
Rheumatoid (ankylosing) spondylitis
Degenerative joint disease (osteoarthritis) of the hip
Gout

Rheumatoid Arthritis

In many patients with chronic rheumatoid arthritis Indocin (indomethacin) produces a significant decrease of pain and stiffness within 48 hours, while in other patients treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occurs. Treatment may be required in chronic rheumatoid arthritis for at least a month before concluding that it has not produced significant benefit.

When a response has been obtained, the daily salicylate requirements can usually be reduced and often stopped. Also, if patients have been receiving corticosteroids, the steroid dosage often can be gradually reduced by 25 to 50 per cent, and in some patients it can eventually be completely discontinued. In such instances the steroid dosage should be reduced slowly.

In acute rheumatoid arthritis, or in acute flares of chronic rheumatoid arthritis, prompt improvement with relief of pain, tenderness, swelling and stiffness will usually occur.

Rheumatoid (Ankylosing) Spondylitis

Indocin (indomethacin) frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

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[1] Registered trademark of Merck & Co., Inc.

Degenerative Joint Disease (Osteoarthritis) of the Hip

Indocin (indomethacin) has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

Gout

In acute attacks of gout the response is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

During the interval phase of gouty arthritis, indomethacin together with adequate doses of uricosuric agent may provide relief of pain and prevent the recurrence of acute attacks.

In these conditions indomethacin may on occasion replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds, and colchicine.

CONTRAINDICATIONS

As with other anti-inflammatory agents, indomethacin may mask the signs and symptoms of peptic ulcer. Indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract. For these reasons it should not be given to patients with active peptic ulcer, gastritis, regional enteritis or ulcerative colitis, and should be used with caution if there is a history of these disorders.

Indomethacin is contraindicated in aspirin-sensitive asthmatics.

The safety of Indocin for use during pregnancy or lactation has not been established.

The drug should not be prescribed for children because safe conditions for use have not been established. In a few cases of severe juvenile rheumatoid arthritis who were receiving Indocin along with other drugs, severe reactions, including fatalities, have been reported.

WARNINGS

Patients who suffer from dizziness, light-headedness, or feelings of detachment on Indocin (indomethacin) should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present.

It should be used with caution in patients with psychiatric disturbances, epilepsy, or parkinsonism, since it may, in some instances, aggravate these conditions.

PRECAUTIONS

Indomethacin should be used with caution if there is a history of ulcer, gastritis, regional ileitis, or ulcerative colitis, because of its potential for causing gastrointestinal tract bleeding.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg. four times a day) produce less fecal blood loss than average doses of aspirin (600 mg. four times a day). Notwithstanding, it may cause single or multiple ulceration of the stomach, duodenum, of small intestine. There have been reports of severe bleeding and of perforation with a few fatalities. Patients may also develop gastro-intestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, discontinue use. In many patients with peptic ulceration a history of a previous ulcer was present or they were on concomitant steroids, salicylates, or phenylbutazone. The possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drugs were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason periodic hemoglobin determinations are recommended.

The gastrointestinal effects may be minimized by giving the drug immediately after meals, with food, or with antacids.

In common with other drugs which have anti-inflammatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must be alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. Indomethacin should be used with caution in patients with existing, but controlled, infections.

As with any new drug, patients should be followed carefully to detect unusual manifestations of drug sensitivity.

ADVERSE REACTIONS

Central nervous system reactions most frequently associated with indomethacin are headache (which, if present, is usually more apt to be severe in the morning), dizziness, and lightheadedness. Infrequently reported reactions include mental confusion, drowsiness, convulsions, depression, and other psychic disturbances such as depersonalization. Central nervous system effects are often transient and frequently disappear with continued treatment or with reduction of dosage. The severity of these effects may, on occasion, require stopping therapy.

Gastrointestinal reactions which occur most frequently are nausea, anorexia, vomiting, epigastric distress, abdominal pain, and diarrhea. Others which may develop are ulceration, single or multiple, of esophagus, stomach, duodenum or small intestine, including perforation and hemorrhage with a few fatalities having been reported; gastrointestinal tract bleeding without obvious ulcer formation: and increased abdominal pain when used in patients with pre-existing ulcerative colitis. Less common gastrointestinal reactions which may occur are stomatitis; gastritis; bleeding from the sigmoid colon, occult in type or from a diverticulum: and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma). Gastrointestinal reactions where it is not known whether the effects can be attributed to indomethacin include development of ulcerative colitis and development of regional ileitis.

Hepatic reactions which have been reported rarely are jaundice and hepatitis.

Cardiovascular-renal reactions which may occur infrequently include edema, elevation of blood pressure, and hematuria.

Dermatologic-hypersensitivity reactions infrequently reported are pruritus, urticaria, angioneurotic edema, angiitis, skin rashes, loss of hair, and acute respiratory distress including sudden dyspnea and asthma.

Hematologic reactions, which may develop infrequently are leukopenia, purpura, and thrombocytopenia. Rarely, agranulocytosis has been reported, but a definite relationship to the drug has not been established. Some patients may manifest anemia secondary to obvious or occult gastrointestinal bleeding (periodic hemoglobin determinations are recommended).

Eye-ear reactions may occur infrequently, such as tinnitus, blurred vision, hearing disturbance, and orbital and periorbital pain.

Miscellaneous adverse reactions rarely reported include vaginal bleeding, hyperglycemia and glycosuria.

DOSAGE AND ADMINISTRATION

Indocin (indomethacin) is available as 25 mg. capsules for oral use.

In chronic disorders treatment should be started with a dosage of 25 mg. two or three times a day. Starting therapy with low doses, with gradual increases when necessary, will produce maximum benefit and minimize adverse reactions. Always give the drug with food, immediately after meals or with antacids, to reduce gastric irritation.

The drug should not be prescribed for children because safe conditions for use have not been established.

Dosage Recommendations for:

1. Rheumatoid arthritis and rheumatoid (ankylosing) spondylitis

Initial dosage.—25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about *weekly* intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

For patients with *acute* rheumatoid arthritis or with *acute flares* of chronic rheumatoid arthritis, increase the dosage *daily* by 25 mg. until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg. is reached. If adverse effects develop as the dosage is increased, it should be reduced to a tolerated level for 2 or 3 days and then gradually increased by 25 mg. every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage gradually to 75 to 100 mg.

Reduction of steroid dosage.—Use of indomethacin often will permit a gradual reduction of steroid dosage by 25 to 50 per cent. In some patients steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

2. Degenerative joint disease (*osteoarthritis*) *of the hip*

Initial dosage.—25 mg. two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg. at about *weekly* intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg. a day is reached. If a satisfactory response is not obtained with 200 mg. a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, decrease to a tolerated level and maintain at that dosage for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg. at about weekly intervals to 150 to 200 mg. a day.

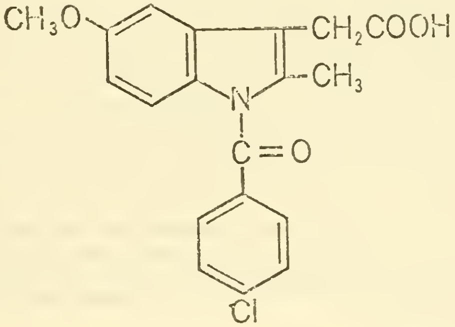
3. Gout

To control acute attacks.—50 mg. three times a day until all signs and symptoms subside. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

To prevent acute attacks.—During the interval phase of gouty arthritis the dosage may be reduced to as little as 25 mg. twice a day, given with an adequate dose of a uricosuric agent such as probenecid.

CHEMISTRY AND PHARMACOLOGY

The chemical name for indomethacin is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid. It has the following structural formula:



Anti-Inflammatory Action

The anti-inflammatory activity of indomethacin was first demonstrated in animals, measuring the ability of the compound to inhibit either granuloma formation or edema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with anti-rheumatic activity in man. Assays of relative potency indicated that indomethacin was more potent than aspirin, phenylbutazone or hydrocortisone; the potency ratios varied with the test employed.

The inhibition of carrageenin-induced edema by indomethacin is specific; the compound failed to inhibit edema induced by a variety of agents other than carrageenin, nor did it reduce edema if drug was administered after the edema had been established.

As with other anti-inflammatory agents, the mechanism of action of indomethacin is unknown. Brodie has postulated that one mechanism might be the displacement of cortisol from binding sites on plasma protein, driving the steroids into the tissues. However, indomethacin is fully active in the absence of the adrenals; and its activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, indomethacin in intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indicators of adrenal activation. The anti-inflammatory activity of combinations of indomethacin and a steroid was greater than that of either drug alone in comparable doses.

Recent experiments have shown indomethacin to have a favorable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or aspirin in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical anti-arthritic activity.

Antipyretic Activity

The antipyretic activity of indomethacin has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats. A direct comparison of peak antipyretic activity in the yeast fever test showed indomethacin to be about 9 times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as aspirin.

The antipyretic activity of indomethacin has been confirmed clinically by observations in patients with a variety of febrile conditions.

Analgesic Activity

Indomethacin is active in animal tests designed to assay analgesic activity of non-narcotic analgesics. Moderate doses raise the response theshold when pressure is applied to the yeast-inflamed foot of the rat, but do not affect responses to thermal stimuli, or to pressure on a non-inflamed foot. Qualitatively, indomethacin behaves like an analgesic of the anti-inflammatory-antipyretic type typified by the salicylates, and not of the narcotic type typified by morphine.

When single oral doses of indomethacin were assayed in the inflamed foot assay, the compound was found to be about 28 times as potent as aspirin and about 14 times as potent as phyenylbutazone.

Toxicology

The oral lethal dose$_{50}$ values were as follows: mouse—50 mg./Kg.; rat—12 mg./Kg.; guinea pig—543 mg./Kg.; rabbit—135 mg./Kg.; dog—>160 mg./Kg. Deaths were delayed and usually occurred between 3 to 7 days following drug administration. In general, dose-response curves were very flat.

Subacute and chronic toxicity studies on indomethacin were conducted in mice, rats, rabbits, cats, guinea pigs, dogs, monkeys (*Macaca mulatta*), chickens, and swine. These studies revealed that the principal toxicologic attribute of indomethacin, in common with other nonsteroid anti-inflammatory agents, was ulceration of the gastrointestinal tract. While some variation in sensitivity of this effect was seen among the various species, this was probably related to differences in metabolism and rate of elimination. An adequate margin of safety (60 to 120 times) was found between effective anti-inflammatory and toxic doses in the rat.

Reproduction and/or teratogenic studies in mice, rats, and rabbits showed no effect on fetal development or the reproduction cycle, although in rats there was some decrease in fetal viability. Studies in mice demonstrated that indomethacin crosses the placental barrier.

Absorption and Excretion

Indomethacin is well absorbed after oral administration in all animals, including man. In dogs, monkeys, rats, and man, peak plasma levels after an oral dose occur within 0.5 to 2 hours. The drug present in the plasma of dog and man is virtually all unchanged indomethacin, but a metabolite (probably the glucuronide conjugate) may be present for the first half hour after intravenous injection in the guinea pig.

The route of excretion is related to the species of animal and is independent of the route of administration or size of dose. Nearly all the compound could be rerecovered in urine and feces. The rabbit eliminates indomethacin almost entirely in the urine, while the dog excretes nearly all the compound in the feces. The rat, guinea pig, monkey, and man eliminate it by both routes. In man, about two-thirds of the drug is excreted in the urine.

In rabbits, rats, guinea pigs, and monkeys, some indomethacin is metabolized by deacylation or demethylation and the metabolites are excreted in the urine as such or as the glucuronide conjugate. In man, however, no evidence of molecular breakdown has been observed, and virtually all of the material excreted in the urine is indomethacin glucuronide.

AVAILABILITY

No. 3316—INDOCIN (indomethacin) capsules, 25 mg. each, are opaque blue and white, imprinted with the MSD trademark and potency, and are supplied in bottles of 100 and 1000.

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(Whereupon, at 1:40 p.m., the subcommittee adjourned, to reconvene tomorrow, Thursday, May 2, 1968, at 10 a.m.)

APPENDIXES

Appendix 1

ARTICLES FROM VARIOUS SOURCES RE DRUG INDOCIN (INDOMETHACIN)

[From Behavioral Science Magazine, Vol. 5, Apr. 27, 1960, pp. 109–135]

"A crystallized tear
From the eye of a deer—
Bitten by a snake—
Made people well.
So who can foretell
What cures placebos make?"

A Contribution to a History of the Placebo Effect

(By Arthur K. Shapiro,[1] New York University College of Medicine)

"Those who forget the past are destined always to repeat it."—Santayana.

INTRODUCTION

Interest in the placebo effect has increased considerably in recent years, more papers on the placebo having appeared in the last four years (35 during 1954–1957) than in all previous years (21 between 1900 and 1954). (See Figure 1.) Indices, journals, texts, and abstract journals are increasingly including the word placebo in their list of references; the word placebo appears more frequently in the title of articles (Table 1); and it is becoming a commonplace in research, as it has been a commonplace in medicine for a much longer period of time. A placebo control is included in double blind studies which also are appearing more frequently in scientific literature.

The sharp increase in "psychiatric"[2] interest in the placebo can be seen illustrated graphically in Figure 1, more articles on this subject having appeared in the last two years (9 during 1956–1957) than in all previous years combined (5 between 1900 and 1956). These last two years have been the only years in which the number of "psychiatric" articles (9) has equaled the number of "non-psychiatric" articles (9). Many of these articles comment on the importance of studying the placebo effect. This increased interest is indicative of an important new trend in psychiatry, medicine, and the other sciences.

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[1] This paper was completed at the Massachusetts Mental Health Center, Boston Psychopathic Hospital, and Harvard Medical School.

[2] The term "psychiatric" refers to psychiatric and psychological articles of interest. The term "non-psychiatric" refers to all other medical specialties and workers in areas such as pharmacology, physiology, etc.

TABLE 1.- NUMBER OF PAPERS INDEXED IN VARIOUS REFERENCES WITH THE WORD "PLACEBO" IN THE TITLE, ACCORDING TO YEAR AND WHETHER THE AUTHOR WAS A "NONPSYCHIATRIC" M.D. (M.D.) OR A "PSYCHIATRIC" M.D. OR PSYCHOLOGIST (PSY.)[1]

Year	Current list of medical literature		Quarterly Cumulative Index Medicus		Excerpta Medica-Neurology and Psychiatry		Digest of Neurology and Psychiatry		Psychological Abstracts	
	M.D.	Psychologist	M.D.	Psychologist	M.D.	Psychologist	M.D.	Psychologist	M.D.	Psychologist
1957								1		
1956	3	3						1		
1955	6			1						
1954	2		5				1		1	
1953	4		3							
1952	1									
1951										
1950	3		1				1			
1949										
1948			1						1	
1947	1									
1946			1							
1945			1							
1944										
1943										
1942										
1941										
1940										
Total	20	3	12	1	0	0	2	2	2	0

[1] References not in existence, available or reviewed are indicated by a blank space. Foreign articles have not been included.

This paper will be concerned primarily with historical considerations. Special emphasis will be placed on the placebo and placebo effect in this history, and on the history of the use of the placebo and the development of the placebo effect concept. Some of the major contributions to an understanding of this concept will be noted and outlined. Some of the conclusions, implications, and questions stimulated by these historical considerations will be discussed.

The paper will not be concerned primarily with the use and ethics of placebos, with the evidence for the existence of the placebo effect, the magnitude of the placebo effect, or an analysis of the placebo effect. It will not be concerned primarily with the theories that have been advanced to explain the placebo effect, or theories which are suggested by the evidence. This will be reported elsewhere (Shapiro, a, b, c).

MEDICAL (NON-PSYCHIATRIC) HISTORY AND THE PLACEBO EFFECT

Let us begin with the "non-psychiatric" medical history. In the following section the "psychiatric" history will be presented.

Sir William Osler (1905) felt that, ". . . the desire to take a medicine is one feature which distinguishes man, the animal, from his fellow creatures." It is probable that whatever beneficial effects accrued to man's first medication could only have been due to the placebo effect (Modell, 1925; Rivers, 1927). This may be defined at the present time as the psychological, physiological, or psychophysiological effect of any medication or procedure given with therapeutic intent, which is independent of or minimally related to the pharmacological effect of the medication or to the specific effects of the procedure, and which operates through a psychological mechanism. Although the pharmacologic effect of a drug may have been deleterious or of little consequence to the organism, its effect could have been beneficial nevertheless. Indeed, this is the history of medical treatment for the most part until relatively recently, since almost all medications until recently were placebos (Houston, 1938; Pepper, 1945).

Patients in ancient Egypt, according to the Ebers Papyrus, in 1500 B.C., were often treated with medication such as "lizard's blood, crocodile dung, the teeth of swine, the hoof of an ass, putrid meat and fly specks" (Findley, 1953). No treatments of specific value are found in all the pages of Hippocrates (Houston, 1938). Despite this, and the continued prescription of the "flesh of vipers, the spermatic fluid of frogs, horns of deer, animal excretions, holy oil" (Leslie, 1954) and other bizarre substances, the physician continued to be a useful, respected and a highly honored member of society.

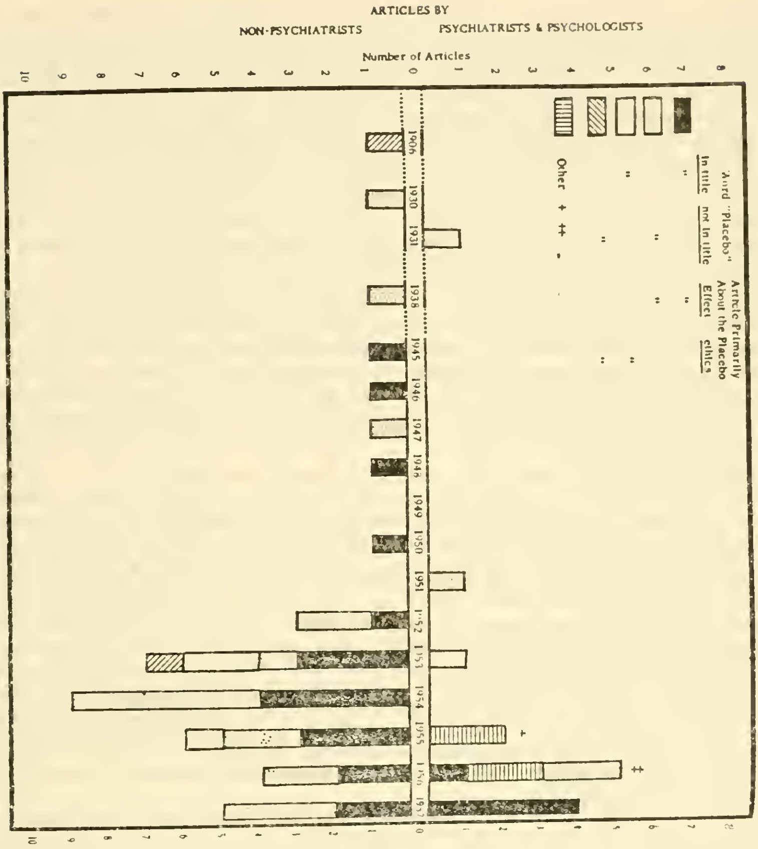

FIGURE 1.—Papers on the placebo effect and ethics according to year and whether the author was a psychiatrist, psychologist, or non-psychiatrist and whether the word "placebo" appears in the title.*

The history of medical treatment concordant with scientific progress in general, is at the same time incredible (Castiglioni, 1946; Garrison, 1921; Haggard, 1929; Haggard, 1933; Haggard, 1934; Goldwyn, 1958; Major, 1954; Major, 1955; Rapport and Wright, 1952; Rivers, 1927; Sigerist, 1958; Zilboorg, 1941). Four of the most famous medications that were used by physicians up to the 16th and at times during the 18th centuries were: the fabled unicorn's horn to detect and protect against poisons in wines, bezoar stones as antidotes for poisons of all types, theriac as a universal antidote, and powdered Egyptian mummy to heal wounds and as an almost universal remedy. These medications were very expensive and only the wealthy could afford them. Unicorn's horn usually came from the ivory of the narwhal or elephant. Bezoar stones, according to legend, were a crystallized tear from the eye of a deer bitten by a snake. In reality, they were a concretion or gallstone found in the stomachs and intestines of animals such as the goat.

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*Criteria for inclusion of papers in this list and references for the various years will be supplied by the author upon request.

†Both articles with placebo in the title and written by psychiatrists but one appearing in a medical journal (Hofling, 1955) and the other in a psychological journal (Abramson et al., 1955).

††Both articles with placebo in the title, one written by a psychiatrist and appearing in a medical journal (Fisher & Olin, 1956), the other written by a psychologist as principal author and a psychiatrist as second author and appearing in a psychological journal (Rosenthal & Frank, 1956).

Theriac dates back to the experiments of Mithradates and was used up to one hundred years ago. Although the main ingredient was the flesh of vipers, it contained 37 to 63 ingredients, all of which were worthless, and which often required several months to concoct. Several official conferences complained about the adulteration of the powdered mummy from Egypt and the impurity of the unicorn's horns. Powdered mummy presumably came from ground-up mummy in Egypt. Mattioli (an antidote containing 230 ingredients), usnea (the moss scraped from the skull of a hung criminal), crocodile dung, fly specs, eunuch fat were only a few of the more palatable drugs. Medical reasoning was primitive: the lungs of the fox were given to consumptives because the fox was a long-winded animal, the fat of a bear, a hirsute animal, was given to those suffering from baldness. Despite the ignorance and superstition, the physician must have benefited his patient because he continued to be held in high esteem.

Consider the treatment that Charles II endured by the physicians of his day: "A pint of blood was extracted from his right arm, and a half-pint from his left shoulder, followed by an emetic, two physics, and an enema comprising fifteen substances; the royal head was then shaved and a blister raised; then a sneezing powder, more emetics, and bleeding, soothing potions, a plaster of pitch and pigeon dung on his feet, potions containing ten different substances, chiefly herbs, finally forty drops of extract of human skull, and the application of bezoar stone; after which his majesty died." (Van Dyke, 1947; for a more complete description, see Haggard, 1929).

Astute observers of their time, such as Montaigne (1946) in the sixteenth century, observed that doctors, in general, were a danger to their patients. Earlier, in the twelfth century, Maimonides (1957), implied this in his statement, "I call him a perfect physician who judges it better to abstain from treatment rather than prescribe one which might perturb the course of the malady." Moliere's satires in the seventeenth century on the medicine of his time are well-known (Garrison, 1921). As late as the seventeenth century, a contemporary of Moliere, Robert Boyle, the father of modern chemistry, after expunging many questionable remedies from the revised pharmacopoeia, included the sole of an old shoe "worn by some man that walked much" was to be ground into a powder and taken for stomach ache (Haggard, 1929). Oliver Wendell Holmes (1891) said as recently as 1860, that nearly all the drugs then in use should be thrown ". . . into the sea where it would be the better for mankind, and all the worse for the fishes." Despite this, sick patients continued to submit to purging, puking, cutting, cupping, blistering, bleeding, freezing, heating, sweating, and shocking.

In 1794, Dr. Ranieri Gerbi, a professor at Pisa, published a manuscript describing a miraculous cure for toothache due to any cause which lasted for a whole year. A worm species, called curculio antiodontaligious, was crushed between the thumb and forefingers of the right hand. The fingers then touched the affected part. An investigatory commission found that 431 of 629 toothaches were stopped immediately. Later, Dr. Carradori, court physician at Weimar, advanced the discovery by substituting a more pleasant ladybird, and an official commission confirmed the immediate relief of toothache in 65–70 per cent of cases. Soon thereafter, an English paper published the following prescription for toothache: "fill your mouth with milk and shake it until it becomes butter, in this way at least three out of four toothaches cease immediately and without fail." (Volgyesi, 1954). This prescription, although pharmacologically ineffective, was more palatable than Pliny's prescription that a mouse be eaten once a month to prevent toothache (Haggard, 1934), or the use of urine as an analgesic mouthwash.

Mistletoe was thought by the ancient druids to have curative virtues against St. Anthony's fire (erysepelas), corns, frostbite, muscular atrophy, apoplexy, infertility, chorea, and bubonic plague (*Spectrum*, 1957, b). It was Galen's drug of choice and thought to be a plant that grows on the oak and hence cannot fall, and naturally should be a specific for the falling sickness (Lennox, 1957). In 1719, however, Colbatch (1719) found it as effective when grown on the lime tree. By the 17th century its powers had spread and it was thought to be effective against edema, impotence, leprosy, syphilis and other diseases. It was thought to be effective against epilepsy from the 17th century and was used by Sir Charles Locock, physician to the queen, who thought epilepsy might be caused by crowded teeth, the practice of onanism, and by a hysterical form connected with the menstrual period (Lennox, 1957)—all of which are completely unrelated to the disease.

A Dr. Raymond at the Salpetriere in Paris found 70 per cent of patients suffering from a variety of diseases, including tabes, were treated successfully by suspending them by their feet, causing the blood to flow into their heads. A collaborator of Bernheim at Nancy, a Dr. Haushalter, reversed the procedure and suspended the patient's head upwards and obtained a similar per cent success in a variety of organic and nervous diseases (Volgyesi, 1954).

One could expand at considerable length on other such examples. Today we know that the effectiveness of these procedures and medications was due to the placebo effect, although little is known about how the placebo effect is effective. Let us continue to explore the historical past in order to learn how not to repeat it.

The placebo effect and the doctor-patient relationship

Although medicine was integrally related to the finest scientific, religious, cultural, and ethical traditions in most periods of history, and despite the ephemeral and/or quite quantitative appearance of drugs or procedures which were truly helpful, one may ask how physicians maintained their position of honor and respect throughout history in the face of thousands of years of prescribing what we now know to be useless and often dangerous medications? Indeed, this would have been a major accomplishment of the physician were it not for the fact that despite the uselessness of the drugs and procedures, nevertheless, the physician truly helped the patient. It was not to the specific medications, however, that the patient responded, but to something inherent in the doctor-patient relationship.[3] Findley (1953) asks, ". . . if it can fairly be said that scientific medicine began only seven or eight decades ago, what of those who practiced before? Were they ignorant, unscrupulous, fraudulent?" He goes on to say, ". . . that the physician is a vastly more important institution than the drug store," and that even today, "Despite the scientific achievements of this century the physician himself is still the most important therapeutic agent." According to Findley, the effectiveness of this placebo effect lies in the action, ritual, faith and enthusiasm on the part of both the doctor and patient.

Houston (1938), in an early article, discusses the doctor as a therapeutic agent, describing early medicine as a symbol related to the placebo effect. He states that in the early history of medicine the relationship between doctor and patient comprised all that the doctor had to offer the patient. The medicines used were placebos, and, "The great lesson, then, of medical history is that the placebo has always been the norm of medical practice, that it was only occasionally and at great intervals that anything really serviceable, such as a cure of scurvy by fresh fruits, was introduced into medical practice. . . . Their skill was a skill in dealing with the emotions of men. They themselves were the therapeutic agents by which cures were effected. Their therapeutic procedures, whether they were inert or whether they were dangerous, were placebos, symbols by which their patients' faith and their own was sustained." He continues, "The history of medicine is a history of the dynamic power of the relationship between doctor and patient. Through centuries when doctors were doing more harm than good this dynamic force has sustained the medical profession in the esteem of their clientele, it has inspired their fellow citizens with such faith in its values that they were willing to give economic support to the doctor." Houston relates the efficacy of the placebo to the faith of the doctor and patient in the medication, to the faith that the doctor is able to impart to the patient, and to the ameliorative effect of action which the doctor provides in some form.

This view is reiterated by Modell (1955): "It would appear that this placebo action is the one constant in the long history of medical practice. It is the one common denominator, for instance, between the treatment of the Egyptian physician who, in the Papyrus Ebers, prescribed a draught of one-thirty-second part of Tail-of-Mouse with Honey, one third, for cooling the anus, and the treatment of the modern physician who prescribes penicillin for pneumonia. Placebo effect was present in the administrations of the first tribal witch doctor and is equally active today, since it is a component . . . not only of medication, but of every phase and kind of medical treatment."

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[3] Another factor contributing to the "success" of these physicians in the past must be considered. Spontaneous recoveries and remissions "can" occur in the course of almost any illness and "may" be unrelated to the administered drugs, doctor-patient relationships and placebo effects. It is very difficult, however, to isolate this factor because of the potential placebo effect in every therapeutic relationship. In addition, the belief of the physician and/or the patient that recovery is a consequence of some activity of the physician would tend to increase the effect of placebos in general. Although this factor must be postulated, it does not negate what is thought to be the more important influence of the doctor-patient relationship in the history of medical treatment.

The frequent reference to the importance of the "art of medicine" implies an understanding of the placebo effect (Bromberg, 1954; Bromberg, 1958; Hailman, 1953; Modell, 1955; Parsons, 1951; Pepper, 1945). Though none of the drugs listed by Hipocrates have proven to be of any usefulness, his observation on the "art of medicine" implies an understanding of the placebo effect and his psychotherapeutic acumen was extremely pertinent (Block, 1957). The famous admonition, loosely paraphrased, "You should treat as many patients as possible with the new drugs while they still have the power to heal," implies a knowledgeable appreciation of the placebo effect, a statement which has become so famous that it has been attributed to Trousseau (Findley, 1953; Koteen, 1957; *Spectrum*, 1957a), Osler (Wayne, 1956), Sydenham (Elkes, 1954) and Nolan D.C. Lewis (Sabshin, 1956). Another historical fact which implies an effect of the placebo has been noted by many authors (Bernheim, 1889; Bromberg, 1954; Grinker, 1958; Horwitt, 1956; Janet, 1925; Sabsin and Ramet, 1956). Findley (1953) says, "One drug after another has its little day of popularity, then sinks into oblivion. Sheaves of paper by well-intentioned authors testify to their usefulness, but they are quickly replaced by others. This familiar phenomen is perhaps the strongest argument for the validity of placebo therapy, for it means faith endows drugs or treatments with powers which they themselves do not possess." The importance of faith is reflected in the fact that one of the best educated, major religious groups in the United States is able to deny the rational efficacy of any treatment or medicine and to assign all treatment benefits to faith. Houston (1938) remarks on the many reminders of the historical past in the contemporary successful existence of the nostrum vendors, chiropractors and myriads of other varieties of quackery. He also notes that no one considers applying the principles of osteopathy to animals, where it would certainly fail, because the principles are effective only when they involve a human interpersonal relationship, [although it is possible that animals are capable of "placebo-like" reactions also (Gliedman, Gantt, & Teitelbaum, 1957; Wolff, 1946)].

When one considers that the normative history of medical treatment, until relatively recently, has been the history of the placebo effect, one is amazed to find a veritable curtain of silence about it. Houston (1938) likens the pages of medical history to the log of an old-fashioned ocean voyage, in which it was noted that on such a day a whale spouted, or a flying fish was sighted, or a bit of driftwood seen, but in which no mention is made of the huge prevailing fact, that what was constantly seen, almost exclusively, was the unending green waste of water. This circumambient ocean is by analogy the placebo effect.

The Countess of Chinchon is erroneously credited with introducing cinchoma bark, which contains quinine, as a treatment for febrile infections in 1638. Sydenham, by demonstrating that it was specific only for fever of malarial origin, contributed to the end of Galenism and the beginning of scientific medicine (Garrison, 1925; Haggard, 1934; Major, 1954; Major, 1955; Pepper, 1945). It may be considered that this was the first drug that was not placebo (Findley, 1953; Houston, 1938; Pepper, 1945) because previous to this there was no way to distinguish a placebo from a non-placebo (Pepper, 1945). But even after this period, and even after the beginning of scientific medicine which began seven or eight decades ago, (Findley, 1953); Rivers 1927; Van Dyke, 1947), one cannot escape noticing the continued resistance to the use of the word "placebo", or the concept underlying the word, in medical parlance, dictionaries, and texts. This is illustrated in the paper by Pepper (1945), which is of interest in that it was the first paper devoted exclusively to the placebo, with the word "placebo" in the title.

History of the word "placebo"

Pepper (1945) eloquently traces the history of the word "placebo" (see also Webster's, 1940, and the Oxford, 1933, Dictionaries). It is the first person singular of the future indicative of the Latin verb "to please"; the word "placebo" itself being equivalent to the phrase "I shall please." The first use of the word dates back to at least the thirteenth century. It appears in the Vespers for the Dead in the Roman Catholic service, the 114th Psalm, in the Vulgate, beginning, "Placebo Domino in regione vivorum. . . ." It was used in the sense of "I will walk before . . ." or "I will please. . . ." It is then found in phrases suggesting sychophancy and servility, and as a noun meaning a flatterer, sychophant or parasite. It was used by Chaucer in both senses, and a character of this type is given Placebo as a proper name. Sir Walter Scott used it in the sense of a soothing sentiment. It is defined as "a commonplace method of medicine" in the 1787 edition of Quincy's *Lexicon* and in the *Philadelphia Medical Dictionary* published in 1808 by John Redman Coxe. Pepper points out that this definition may illustrate the earliest stage of doubt concerning the efficacy of prescriptions of those days, and an approach to the frank admission of a quarter of a century later which appeared in the 1811 edition of Hooper's *Medical Dictionary* with the definition of the placebo as "an epithet given to any medicine adopted more to please than to benefit the patient."

Thus the placebo appears in medical terminology five hundred years after it was first used in other ways. Let us not be too surprised at this belated appearance, because despite the placebo being freely prescribed during the nineteenth and twentieth centuries, the word placebo did not appear in the index of H. C. Wood's *Therapeutics* whose fourteen editions covered the period from 1875 to 1908, and because, as we shall see later, the resistance to and silence about this important therapeutic agent continues into the more recent history of the placebo.

Placebo effect before 1900

Difficulties are encountered when reviewing the literature prior to 1900. This literature is massive and the indexing is inadequate. The terms placebo and placebo effect were hardly used prior to 1900. This review, therefore, cannot be extensive or exhaustive.

There are, however, many indications that physicians and others of the past (even from earliest times) were cognizant of "placebo-like" phenomena, although this was not referred to as the placebo effect, exhaustively studied or extensively written about. Certainly the full implications of this phenomena were not appreciated.

The observations of Maimonides, Montaigne, Moliere, and Trousseau have been mentioned previously.

Pierre Pomponazzi, an Italian philosopher, uttered these words in the 16th century: "We can easily conceive the marvelous effects which confidence and imagination can produce. . . . The cures attributed to the influence of certain relics, are the effect of this imagination and confidence. Quacks and philosophers know that if the bones of any skeleton were put in place of the saint's bones, the sick would none the less experience beneficial effects if they believed that they were near veritable relics." (Tuke, 1886).

Paracelsus commented in the fifteenth century: "Whether the object of your faith be real or false, you will nevertheless obtain the same effects. Thus, if I believe in St. Peter's statue as I would have believed in St. Peter himself, I will obtain the same effects that I would have obtained from St. Peter;—but that is superstition. Faith, however, produces miracles and whether it be a true or a false faith, it will always produce the same wonders." (Charpingnon, 1864).

It should be noted, however, that these observations are directed not to medical practice, but to religious faith and mysticism as treatment. To Paracelsus' credit belongs his vitriolic opposition to the polypharmacy of his day, the observation that medicine killed and that nature heals. He, however, espoused his own brand of occultism and clung to his own placebo medication, e.g., sympathetic powder, which cured the injuries of a wounded person when applied to the blood-stained garments (Garrison, 1921). Paré was notable for his contributing to the abandonment of many venerable beliefs, e.g., Egyptian mummy, unicorn horn, bezoar stones and boiling oil for cauterization of wounds. He substituted his own placebo for the latter eventually with a concoction consisting of earthworms steeped in turpentine and oil of puppies and lillies (Garrison, 1921).

Oliver Wendell Holmes (1891) first presented his very interesting lecture on *Homeopathy and its Kindred Delusions in 1842*. Although his main concern is with a criticism of homeopathy, he discusses the Royal cure of the King's Evil, the Weapon Ointment, Sympathetic Powder, the Tarwater panacea of Bishop Berkeley and Perkins' Metallic Tractors. He asseverates how patients can benefit "through the influence exerted upon their imaginations," and how they, "all display in superfluous abundance the boundless credulity and excitability of mankind upon subjects connected with medicine." He examines these phenomena in order to illustrate the ease with which numerous *facts* are accumulated to prove the most fanciful and senseless extravagances, and the inefficiency and incompetency of persons without medical knowledge despite wisdom, honesty, and accomplishment. He is cognizant of the role of spontaneous remission in the natural course of disease, citing a figure of 90 per cent recovery in patients seen in general practice, "provided nothing were done to interfere with the efforts of nature." He is familiar with elemental probability theory and mentions several primitive attempts at controlled studies.

Although Holmes does relegate the majority of drugs then in use to the bottom of the sea, for the most part, he addresses himself to the abuses of the past and those at the periphery of medicine, and not to the mainstream of medical practice of his day. However, there are some implications that he does address himself to the medical practice of his day indirectly and by analogy. This is implied to some extent in the article and especially in the preface to the article.

Although many authors in the past (as today) have given some indication that they were cognizant of "placebo-like" effects (the degree of sensitivity varying considerably), it is striking how this was no guarantee against them becoming subject to a belief in a placebo of their own.

This is dramatically illustrated by the cogent observation of Quimby in 1859, who said, "But through a great many mistakes, and the prescription of a great many useless drugs, I was led to re-examine the question, and came in the end to the position I now hold: the cure does not depend upon any drug, but simply upon the patient's belief in the doctor or the medicine." (Janet, 1925). P. P. Quimby was the immediate predecessor of Mary Baker Eddy and Christian Science.

Paré believed in the puppy ointment and Paracelsus espoused occultism. Trousseau, who was able to say "You should treat as many patients as possible with the new drugs while they have the power to heal," was able to claim diseases (such as neuralgia, nervous dyspnoea, angina pectoris and rheumatism) to be cured, modified and rapidly checked by the use of magnets "which it is impossible to refer to the patient's imagination" (Trousseau, 1833).

William Osler was a therapeutic nihilist who battled the irrational polypharmacy of his day. When discussing "Psychical methods of cure, in which faith in something is suggested to the patient," (Osler, 1892), he approvingly quotes Galen as saying, "he cures most in whom most are confident," and Paracelsus encouraging his patient "to have a good faith, a strong imagination, and they shall find the effects." He continues, "Faith in the gods or in the saints cures one, faith in little pills another, hypnotic suggestion a third, faith in a plain common doctor a fourth. . . . Faith in us, faith in our drugs and methods, is the great stock in trade of the profession . . . the touchstone of success in medicine . . . and must be considered in discussing the foundation of therapeutics . . . a most precious commodity, without which we should be very badly off." He points out that doctors do not enjoy a "monopoly in the faith business," and that, "While we doctors often overlook or are ignorant of our own faith-cures, we are just a wee bit to sensitive about those performed outside our ranks." Despite the latter, Osler used cupping, leeching and venesection (and other doubtful medicinal substances) in the treatment of pneumonia, stating, "a timely venesection may save life . . . relieving the pain and dyspnoea, reducing the temperature, and allaying the cerebral symptoms" (Osler, 1892).

It is appropriate to remember the wise words of Janet (1925): "It is only too easy to make fun of stories of miraculous cure. Not merely are skeptics prone to use this weapon of ridicule, but the faithful do the same thing. The devotees of a religion are strongly inclined to attack kindred superstitions. Nothing will persuade the adepts of Lourdes that the miracles worked at the shrine of Aesculapius were genuine. Who could induce the admirers of animal magnetism to take a serious view of such miracles as those of Lourdes: Each one attacks his neighbor, and is quite unaware that his criticisms rebound upon himself."

Placebo effect from 1900 to 1945

Very few articles were written on the placebo between 1900 and 1945. It is difficult to trace such articles because the topic has never been indexed in the Index of the Surgeon General's Library, and not in the Quarterly Cumulative Index Medicus prior to 1945, or in the Current List of Medical Literature prior to 1946. (Table 1) One would have to scour mountains of literature to completely cover the literature during this period. This literature was covered, insofar as it could be, by tracing each reference to its source that came to the author's attention, and by reviewing subjects such as the doctor-patient relationship, therapeutics, faith cures, and suggestibility. Several articles were found which discussed the placebo and placebo effect and which characteristically did not have the word placebo in the title.

Cabot (1906) discusses the ethics of the "Nostrum Evil" referring to the placebo as quackery. In the same year, Fantus (1906), in his text on pharmacy and prescription writing, briefly mentions the positive indications for the use of placebos.

Rivers (1908) studied *The Influence of Alcohol and other drugs on Fatigue* in which he used inert material, not referred to as a placebo, as a control. The latter was designed to taste and appear indistinguishable from the experimental drug. The subjects, or when the experimenter was a subject, had no knowledge of the substances they were receiving. It is one of the earliest anticipations of the double blind procedure. Many methodological variables are considered. It represents a very early understanding of (and greater sophistication than many contemporary investigators about) some of the powerful effects of the placebo in experimentation. It is interesting that no statisical analysis was made of the extensive data, because as recently as 1908 this methodological tool was unavailable. Rivers' (1927) erudition and prescience again appears in his posthumous *Medicine, Magic and Religion*, which was written for the most part prior to 1920. He says, "The action of suggestion can never be excluded in any form of medical treatment, whether it be explicitly designed to act upon the mind or whether ostensibly it is purely physical in character. . . . If we confine our attention to our own culture, it is only within the last fifty or sixty years that there has been any clear recognition of the vast importance of the mental factor in the production and treatment of disease, and even now this knowledge is far from being fully recognized either by the medical profession or the laity. . . . Though remedies acting through the mind were probably the earliest to be employed by Man, the knowledge that the remedies act in this way is one of the most recent acquirements of medicine. . . . Few can now be found who will deny that the success which attended the complex prescriptions, and most of the dietetic remedies of the last generation, was due mainly, if not entirely, to the play of faith and suggestion. The salient feature of the medicine of today is that these psychical factors are no longer allowed to play their part unwittingly, but are themselves becoming the subject of study, so that the present age is seeing the growth of a rational system of psychotherapeutics."

Ayman (1930) discusses the concept of the placebo without mentioning the word in a splendid paper in which he evaluates the therapeutic results in 35 papers on essential hypertension. He found that in every paper complete or partial symptomatic relief was described. Up to 85 per cent reduction in blood pressure was reported. Mistletoe, diathermy, watermelon extract, and Nauheim baths were some of the therapeutic agents listed. Ayman treated forty patients with drops of dilute HCl t.i.d. and 82 per cent showed definite improvement. Many minor and some major side effects were reported. Ayman believed that the common element was the enthusiastic giving or doing of something to the patient.

Much of the material in the very fine article by Houston (1938) has been mentioned previously. In addition, the word "placebo" is used extensively, and some of the factors involved in the placebo effect are discussed. Fantus (1938) expands in greater detail on his previous statement in 1906. He again advises candor and psychotherapy where possible, but briefly discusses the situations in which placebos are indicated—patients with low intelligence and imaginary illnesses. He decries the use of expensive placebos and the widespread use of medication such as vitamins that are prescribed in the spirit of the placebo.

No other articles have come to the author's attention prior to 1945 except for those by psychiatrists which will be discussed later.

As can be seen from Figure 1, prior to 1952, there was less than one article on the placebo effect per year. Despite the demonstration by Ayman as early as 1930 that studies on hypotensive agents were subject to the placebo effect, the vast majority of articles and most research, even up to the present day, is conceived, executed, and reported without adequate controls, indicating a failure to appreciate the powerful effects of the placebo. Some of the variables in research on hypotensive agents have been pointed out in recent articles by Schapiro, Myers, Reiser, and Ferris (1954) and Schapiro (1955). During the last twenty years, not only has the literature on the placebo effect been surprisingly meager, but the principles that follow such understanding have not been absorbed into the mainstream of medical research and practice (Hailman, 1953). The placebo is not indexed or discussed in LaWall's *Four Thousand Years of Pharmacy* (1927) or, as pointed out by Pepper, in modern books on treatment. An issue of the *Memphis Medical Journal* (1941) is devoted to an evaluation of drugs, which included ten articles on the use and abuse of cathartics, vitamins, hormones and other drugs. The word "placebo" is not mentioned though some of the concepts implicit in an understanding of the placebo effect are discussed.

In 1938 one hundred million dollars was spent by the American public for vitamin preparations. The total amount spent on medical care in the same year was approximately one billion dollars (Sanford, 1941). Thus, approximately 10 per cent of the nation's medical expenses was spent for vitamins, which are so often prescribed both knowingly and unknowingly for their placebo effect (J.A.M.A., 1959). Dunlap, Henderson, and Inch (1952) analyzed over 17,000 prescriptions of physicians from representative areas in Great Britain for a one month period. Approximately one third were considered to be in the placebo category. The *British Medical Journal* (1952) editorialized that, ". . . a bottle of medicine is given as a placebo in about 40 per cent" of the patients seen in general practice, a figure that is close to Cabot's (1906) estimate of 44 per cent of the prescriptions filled by Boston Back Bay drug stores.

Recently the influence of size, color, and taste on the effectiveness of placebos has been discussed, although it should be remembered, that "What constitutes a good placebo cannot be specifically stated, because what may be good for one patient may not be so for another even though he has a similar condition" (J.A.M.A., 1955).

Leslie (1954) discusses the influence of color on the effectiveness of placebos, advising red, yellow, or brown rather than blue or green which are associated with "poisonous or external-use-only liquids." The use of red coloring agents, such as alkaline aromatic solution, has long been standard prescription practice, and officially sanctioned by the United States Pharmacopoeia and the National Formulary. He feels that size is also important, tiny and oversize tablets and capsules being much more impressive than average sized ones, ". . . the tiny ones suggesting great strength and the jumbo ones impressing by its heroic size." The more a tablet resembles aspirin the less effective the psychological effect. It is probable that prescribing nine or eleven drops rather than the usual ten would add to the effectiveness of the placebo effect. Taste has always been important. The aromatic elixir (Wolff, 1946), the compound tincture of gentian (Dubois, 1946; Findley, 1953; Leslie, 1954; Wolff, 1946), and asofetida were standard bitter placebo medications used in the past. A more contemporary bitter solution can be prepared with a 0.1 per cent solution of sodium dehydrocholate. Wolff (1946) finds the ammoniated tincture of valerian to be a very efficacious placebo because of "the riot of tastes and smells in the preparation." It may be pointed out that the simple lactose tablet has fallen into disuse because it can be easily recognized and because it can be tasted and the prescription easily read and interpreted. How much more effective is a strange-tasting drug with a complicated and esoteric appellation?

The gastro-intestinal tract, from one end to the other, has been especially prone to exploitation by the placebo. It would be superfluous at this time to name the hundreds of placebo medications that have been used and continue to be used in the treatment of dyspepsia, gastric distress, irritable bowel, bulemia, constipation, and even for conditions such as peptic ulcer. Purgatives and enemas were known and used prior to Hippocrates. Louis XIII was so enthusiastic about their usefulness that he prescribed them for his hunting dogs. Voltaire advised young men to secure a wife who could give an enema pleasantly and quickly (Seager, 1941). When one considers the limited advantages and probable harmful consequences of emptying the intestinal tract, such as, dehydration, exhaustion, discomfort, loss of nutrition, disturbance of sleep and even possibly death (the mortality from appendectomy being 10 per cent greater if a purgative is taken prior to operation), it is difficult to understand the continued use of these substances (Campbell, 1941). Advertisements for colonic irrigations are seen frequently in most daily newspapers. The expenditure for proprietary drugs of this sort must reach millions of dollars.

The odor of tincture of benzoin makes the inhalation of steam so much more acceptable to patients. The effectiveness of placebos on allergic rhinitis, hay fever, and other nasal conditions is well-known. Headaches respond flagrantly to placebo medication. The effectiveness of Epsom salts used in wet dressings for inflamed areas is not due to the magnesium sulfate which is the active ingredient, because this has no specific cutaneous effect. This is also true of the methyl salicylate used in numerous preparations for sore muscles. Both are effective by virtue of their placebo effect (Leslie, 1954; Hyman, 1946).

The so-called tonics in medicine are notorious placebos. The most active part of the tincture of condurango, a bitter tonic and stomachic, and the fluid extract of cimicifuga nigra, a tonic and antispasmodic, is in their impressive names. Tonics of more recent vintage are the elixir of iron, quinine and strychnine (Findley, 1953; Gold, 1946). Some of the most widely used drugs today are prescribed both knowingly and unknowingly for their tonic or placebo action. Those drugs that are given in inappropriate circumstances or inadequate dosages can be designated as placebo medication. These would include all tonics and most of the vitamin, liver, hormone preparations and a host of proprietary medications, drugs which stimulate and sedate the patient, control and stimulate appetite, the many combinations of drugs with opposing action (the "if-in-doubt" medication) which have recently appeared, and even many potent drugs.

Placebo effect since 1945

The placebo effect is not a phenomenon limited to the past. Dubois (1946) points out that, "You cannot write a prescription without the element of the placebo. A prayer to Jupiter starts the prescription, and it carries the weight of two or three thousand years of medicine" (Findley, 1953; Houston, 1938; Gold, 1946; *Lancet*, 1954; Leslie, 1954; Modell, 1955; Whitehorn, 1958; Wolff, 1946). The prescription is written by the doctor, and although the Latin of the past is disappearing, the polysyllabic names remain. It is then taken to special stores to be filled by specially trained men and is frequently expensive. Any treatment procedure, including all medication, even potent and pharmacologically effective medicines, have potential placebo effects inherent within them (Dubois, 1946; Findley, 1953; Houston, 1938; Gold, 1946; Hyman, 1946; *Lancet*, 1954; Leslie, 1954; Modell, 1955; Pepper, 1945; Rivers, 1927; Whitehorn, 1958; Wolff, 1946).

Let us trace the further development of the word itself.

Dubois (1946) lists three classes of placebo. The first is the pure placebo, such as lactose, which has no possible intrinsic action. The second is the impure or adulterated placebo which contain some active ingredient but which has no effect on the patient's disease. The third is not a placebo itself but is the psychotherapeutic element inseparable from any medication.

Gold (1946, 1954) (who was either responsible for or one of the earliest to use the term "blind-test" for what later became the "double blind procedure," and who has been a major influence in bringing the placebo to the attention of the medical profession) and Clark (1946) view the placebo as a chemical device for psychotherapy.

Gaddum (1954) feels that the placebo is defined as a medicine given more to please than to benefit the patient, and as such, is given to have an effect. He proposed the use of the "dummy tablet" instead, as a form of treatment which is intended to have no effect, which does not aid therapeutic suggestion or work through a psychological mechanism. Beecher (1956 a) differs with Gaddum, feeling that although the word lacks precision it is adequate. Gaddum's idea has not been absorbed into the literature to any extent.

Leslie (1954) widens the definition: "A placebo is a medicine or preparation which has no inherent pertinent pharmacologic activity but which is effective only by virtue of the factor of suggestion attendant upon its administration. The substance may be ingested, injected, inserted, inhaled or applied." Leslie thus adds preparations that are applied to the list of placebos. He also offers a mechanism, suggestion, as part of his definition.

Beecher summarizes the purposes and uses of placebos, ". . . as a psychological instrument in the therapy of certain ailments arising out of mental illness, as a resource of the harassed doctor in dealing with the neurotic patient, to determine the true effect of drugs apart from suggestion in experimental work, as a device for elimination of bias not only on the part of the patient but also, when used as an unknown of the observer, and finally, as a tool of importance in the study of the mechanism of drug action."

Findley (1953), quoting Houston, divides placebos into three types: 1. The type of drug which the physician knows to be inert, but which the patient believes to be potent. 2. Both the patient and the physician believe the drug to be potent, but which is really inert. 3. The patient and the physician both believe a drug to be helpful but which is actually harmful. Findley's concern is with the failure of some physicians to recognize that they are prescribing placebos, and with the harmful effects which may result.

Despite the aforementioned, the usual definition of the placebo, though with some variation, is similar to that appearing in Dorland's *American Illustrated Dictionary* (1951), where it is defined: "An inactive substance or preparation formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of drugs" (Blackeston's, 1956; Oxford, 1933; Shorter Oxford, 1944; Skinner, 1949; Webster's 1956). This definition is interesting in that it harbors a projective mechanism. Patients are not pleased or gratified by the taking of placebos. It is the doctor who invests the giving of placebos and those patients responding to placebos with a variety of feelings which involve guilt and/or hostility, and which are then projected onto the patient and rationalized as the patient being pleased or gratified. An improved definition of the placebo appears in English and English (1958): "A preparation containing no medicine (or no medicine related to the complaint) and administered to cause the patient to believe he is receiving treatment." However, this definition is inadequate also because it fails to mention that anything offered with therapeutic intent may be a placebo, whether it be given with or without the conscious (or unconscious) knowledge of the doctor or therapist.

Although the placebo is old in history, its use in controlled studies is new and appears frequently in contemporary definitions (*Brit. Med. J.*, 1952, Dorland, 1951; *J.A.M.A.*, 1955; Skinner, 1949).

Beecher, Wolf and Lasagna are of considerable importance to the history of the placebo effect. Beecher (1952; 1955; 1956 a; 1956 b; 1957; Beecher, Keats, Mosteller, & Lasagna, 1953) believes the effectiveness of placebos to be related to the degree of stress or anxiety, the placebo modifying the subjective response to an original sensation or by effecting the reaction component of stress. Wolf's (1950) classic experiments with "Tom" which demonstrated how placebos could reverse the pharmacologic action of drugs and cause end organ changes was an early experimental stimulus to the study of the placebo effect. He showed how placebos could cause extensive "toxic" reactions (Wolf and Pinsky, 1954), and experimentally explored other attributes of placebos (Abbot, Mark, & Wolf, 1952; Hagans, Doering, Ashley, & Wolf, 1957; Wolf, Doering, Clark, & Hagans, 1957). Lasagna has contributed important papers (Beecher et al., 1953; Lasagna, Mosteller, von Felsinger, & Beecher, 1954; von Felsinger, Lasagna, & Beecher, 1955; Lasagna, 1956).

The increased interest in the placebo effect is evident from the data in Figure 1 and Table 1. Articles on the placebo effect have even begun to appear in commercial pharmaceutical journals (*Physician's Bull.*, 1955a, 1955b; *Spectrum*, 1957a). Methodological problems (and the placebo effect indirectly) are explored with increasing frequency in medical journals. Books now contain full chapters on the placebo (Modell, 1955; Hollander, 1958).

The belated interest in the placebo effect

Many authors have commented on the surprising belated interest in the placebo effect. Its potency, widespread use, and therapeutic potentialities have not been acknowledged until recently. Study of its underlying mechanism and dynamics have begun to appear relatively late in the history of medicine.

Houston (1938) wonders how the placebo effect, which is so omnipresent, could have escaped scientific notice for so long a period of time. Pepper (1945) points to the resistance against recognition of the placebo effect that has existed throughout the ages, including the period up to 1945. Dubois (1946) states, ". . . the study of the placebo is the most important step to be taken in scientific therapy." He continues, ". . . although placebos are scarcely mentioned in the literature, they are administered more than any other group of drugs . . . that although few doctors admit that they give placebos, there is a placebo ingredient in practically every prescription . . . that the placebo is a potent agent and its actions can resemble almost any drug." Findley (1953) states that the placebo is the most important therapeutic weapon in the hands of even the modern physician. Leslie (1954) is surprised, ". . . that in the light of their importance and everyday use placebos have until so recently been all but neglected in medical curricula and writings." Lasagna (1956) says, "Considering how profound an effect placebos have . . . it is surprising how little study has been given to identifying the characteristics of placebo reactors." Wayne (1956) comments on the little interest that has been taken on the action of placebos. *Lancet* (1954) editorialized, "Our predecessors paid little attention to such a lowly menial, and published references to it were few. But the spread of scientific methods to the study of materia medica has led to a remarkable improvement in the status of . . . the placebo which until recently . . . has never been regarded as quite respectable."

The situation has changed since 1952 as can be noted from Figure 1. More than seven articles on the placebo have appeared each year since 1953. The word "placebo" itself appears more frequently in articles on the placebo effect specifically, and in titles of articles of all types (Table 1).

Factors responsible for the belated interest in the placebo effect

There are several possible factors for the belated interest in the placebo effect. The first possibility is that there is a preconscious (or unconscious) perception of the placebo effect which is not verbalized or acknowledged because its revelation would be anxiety provoking or threatening. This is based on the premise that a consideration of the placebo effect has long been obvious and overdue. The energy required for this suppression (or repression) is derived from anxiety related to loss of self esteem and guilt. Placebos are often given to demanding and difficult patients, when the physician is frustrated personally and professionally, when the physician's knowledge, or medical knowledge in general, is inadequate to the presenting problem, when the doctor-patient relationship is deteriorating, when the physician is in a hostile, punitive or disdainful frame of mind, when too busy to do anything else and when there is nothing else to do because of failure to respond to the usual therapeutic attempts. Physicians often prescribe with the full knowledge, or at least the suspicion, that these substances are placebos, although communicating to the patient, by omission, or commission, that these inert substances are active. The resultant defensiveness and feelings of guilt would add to the difficulty of discussing the placebo with equanimity and carry over to the placebo effect also (Clyne, 1953; Hofling, 1955; Whitehorn, 1958). It may be threatening for some to give up therapeutic methods, abilities or beliefs which required many years to develop and acquire. Others may be threatened by a real or imagined loss of self esteem and prestige among colleagues and in the community and by the threat of uncertainty or loss of magical powers. [Parsons (1951) speaks of the latter in positive terms. He believes that "optimistic biases" are very general and fundamental in human social organization, and are responsible for the pseudo belief in the efficacy of measures, and the magical beliefs and practices that cluster about situations wherein there is an important uncertainty factor and strong emotional interests in the force of action.]

Another factor may be lack of knowledge or rigidity in thinking. If there is no understanding that there is a phenomenon such as the placebo effect, and that all medication has a placebo effect in part, the concept cannot be considered. The consequences are as harmful today as they were in medicine prior to the seventeenth century when it was not known that the effectiveness of almost all medication was due to placebo effect. A third possibility is an understanding of the placebo effect but a belief that it is unimportant or inadvisable to discuss it. We cannot accept this possibility as plausible, the purpose of this paper being to indicate the converse proposition. The last two factors may be a consequence of the first factor, i.e., the threatening nature of the material making it possible for lack of knowledge, the rigidity in thinking, a belief in the unimportance of and the inadvisability of discussing the placebo.

Factors responsible for the recent interest in the placebo effect

How can we account for the recent increased interest in the placebo effect? Scientific knowledge has continued to increase geometrically. This increase in knowledge includes an understanding of the placebo effect. With the increased number of therapeutically effective drugs there is less of a necessity to rely on drugs with a placebo effect. As a consequence the resistance against acceptance of this phenomenon decreases. Individuals are less threatened and the silence about the placebo effect begins to vanish. Another factor may be the repetitious fanfare heralding the effectiveness of new drugs with which the drug companies are increasingly flooding the market. The vast majority of these preparations are relegated to silent oblivion. Repeated experiences of this nature should influence one's thinking about the placebo effect as a consequence. Public and private financial support of research has increased enormously in recent years. Between 1952 and 1955 alone, there has been a fiscal increase of 77 percent in government support of life-science research and an increase of 33 percent in the number of projects (Consolazio and Jeffrey, 1957). Many more individuals are involved in research. The production of scientists, as reflected in the number of doctorates granted each year, has roughly doubled each decade (National Academy of Sciences, 1958). Methodological problems are examined. The placebo effect cannot be ignored.

The influence of psychiatric thinking on the sciences has increased following World War II. Psychologically, psychoanalytically, and socially oriented psychiatrists have entered the medical schools and hospitals in increasing numbers. There is more interdisciplinary contact and research. It should not be surprising that their concern with psychological factors, symbolism, the doctor-patient relationship, transference and counter-transference should influence scientific thinking in the direction of recognizing the extensiveness of psychological phenomena. Psychiatrists have been active in extending their knowledge to the rest of the medical profession and especially to the general practitioner. This is reflected in the numerous lectures, conferences, and books, as well as numerous articles which are directed toward the general practitioner or other medical specialist (Blaint, 1955; Clyne, 1953; English, 1930; Fisher, 1956; Hofling, 1955; Levine, 1942; Romano, 1952; Salfield, 1953).

Despite this, it is dificult to document because psychiatrists (and psychologists) have published the least number of articles on the placebo effect, and only in recent years have they been concerned with it at all (See Figure 1 and Table 1).

PSYCHIATRY AND THE PLACEBO EFFECT

Placebo effect as a problem in psychiatry

Psychiatry is in greater need of the knowledge and of the principles underlying and stemming from the placebo effect than medicine or the other sciences. Psychiatrists manage patients with psychological problems almost exclusively, and are involved in a much more meaningful and closer doctor-patient relationship, a situation which maximizes the placebo potential.

The need for psychiatry to be concerned with the placebo effect is readily apparent from a view of the literature on almost any aspect of psychiatry. Contradictory reports abound in all areas. Although it is not the purpose of this paper to review the literature on threapy and other aspects of psychiatry, some of the highlights should be mentioned. In the treatment of manic depressive psychosis, Bellak (1952) lists fifty odd methods, nearly each one having ". . . been reported as leading to recoveries and/or improvements." Some of the methods of treatment were: testicular vein blood serum, "own blood" injections, lysate of the hypophysis, epivector serum, refrigeration, aurora-tone films, puppets, and diencephalic radiation. The history of the treatment in schizophrenia is even more impressive in this respect (Bellak, 1948). Horwitt (1956) points out how the papers reporting the pathology of schizophrenia year after year, repeated by each new generation, ". . . would make the schizophrenic patient a sorry physical specimen indeed; his liver, brain, kidney, and circulatory functions are impaired; he is deficient in practically every vitamin; his hormones are out of balance, and his enzymes are askew." One can find support in the literature for every possible viewpoint about psychiatric treatment. Many papers have appeared which question the efficacy or the possible placebo-like component of psychotherapy (Appel, Lhamon, Myers & Harvey, 1951; Frank, Gliedman, Imber, Nash & Stone, 1957; Gliedman, Nash, Imber, Stone, & Frank, 1958; Grinker, 1958; Imber, Frank, Nash, Stone, & Gliedman, 1957; Lewis, 1941; Levitt, 1957; Murphy, 1951; Rosenthal and Frank, 1956; Smith and Wittson, 1957; Whitehorn, 1958), electric convulsive treatment (Brill, Crumpton, Eiduson, Grayson, Hellman, Tichards, Strassman, & Unger, 1957; Bond, & Morris, 1954; Karagulla, 1950; Roth, 1952; Zubin, 1953), insulin coma treatment (Ackner and Harris, 1957; Bourne, 1953; Bourne, 1958; Boardman, Lemas, & Markowe, 1956; Boling, Ryan, & Greenblatt, 1957; Fink, Shaw, Gross, & Coleman, 1958; Leyton, 1953) or the other somatotherapies and psychotherapies in general (Appel et al., 1951; Boardman et al., 1956; Bourne, 1957; Clyne, 1953; Diethelm, 1936; Hastings, 1957; Laties & Weiss, 1958; Staudt & Zubin, 1957; Tibbetts and Hawkins, 1956).

The papers illustrating the unresolved position of the drugs are too numerous to mention. There are between 20 and 30 tranquilizers on the market, each purporting to be effective in the treatment of psychological illness, not to mention variants of the latter, the numerous combinations of the latter with other drugs and the recent rash of stimulant drugs. The tranquilizers are the fastest growing drugs in history, and it was estimated that in 1957 they would move into second place in sales, reaching about forty million prescriptions totalling 175–200 million dollars in retail sales (Plumb, 1957; Bello, 1957).

Will we appear as wise one hundred years from now as do the compilers of the Paris Pharmacologia of a century ago who said, "What pledge can be afforded that the boasted remedies of the present day will not, like their predecessors, fall into disrepute, and in their turn serve only as a humiliating memorial of the credulity and infatuation of the physicians who recommended and prescribed them?" (LaWall, 1927). Perhaps recent psychiatric developments in the history of the placebo will gainsay us a place in history as prescient as the Paris compilers of a century ago.

The belated interest of psychiatrists in the placebo effect

Before outlining the contributions of psychiatrists and psychologists, it should be noted that the later have been the last to become interested in the placebo effect. Without going into the details of Figure 1, here are only 2 papers by Americans which meet the criteria of being written by psychiatrists. wtih placebo in the title and appearing in American psychiatric journals. A total of 6 indexed papers with placebo in the title by psychiatrists (Table 1) contrasts with the 36 papers by non-psychiatric physicians.

Although one could object that part of the discrepancy can be accounted for by the comparative preponderance of non-psychiatric investigators this cannot account for the greater part of the discrepancy. One would expect the placebo effect to be more the concern of psychiatrists than of other investigators, and reflect itself in articles on the placebo effect and perhaps in articles with the word placebo in the title. By analogy, one does expect and does in fact find more articles on schizophrenia by psychiatric authors than by others.

This situation is again reflected in the most widely known book on the history of psychiatry. Zilboorg (1941) does not mention the placebo or the placebo effect in his *History of Medical Psychology*. There is no discussion of suggestibility which at times is equated with the placebo effect. There is only a very brief and inadequate discussion of the doctor-patient relationship from this viewpoint. This is true also of Lewis (1941) *A Short History of Psychiatric Achievement*. Some general histories of medicine do slightly better in this respect although they too are inadequate for the most part. Bromberg (1954) acknowledges the importance and effectiveness of faith in the magico-religious psychotherapy of the past in his history of psychotherapy. *Man Above Humanity*. He does not discuss, however, faith, suggestibility, or the placebo effect as it applies to medication prescribed in the past or present or to contemporaneous treatment in psychiatry. Parsons (1951) is far more at home with "placebo-like" phenomena in the therapeutic process (although he does use the term specifically) than the aforementioned authors. He discusses medical practice by way of illustrating a theory of social structure in *The Social System*. Perhaps, because he is a sociologist looking at the therapeutic process from the outside, he can be so much more cognizant of these factors than psychiatrists who are a part of the very process they are observing.

Prior to pursuing this study it was thought that psychologists, by virtue of their careful concern with variables in experimentation, would be cognizant of the placebo effect as an important variable. The converse was found to be true. as indicated by the sparsity of articles published by psychologists (Figure 1) and by the few articles appearing in "Psychological Abstracts" (Table 1). This was further confirmed by the impression that the double blind procedure, which implies an understanding of the placebo effect and which is increasingly being used in clinical studies, is virtually an unknown and unused concept among experimental psychologists who are among the most careful of investigators. Many studies, especially those about which there is some contention, would benefit from a re-evaluation with attention given to this variable.

Psychiatric surprise at the scarcity of articles on the placebo effect

A common feature among psychiatric authors who have written about the placebo effect in recent years is the manifestation of surprise at the scarcity of articles on this subject. It implies that the placebo effect was known but that nobody did anything about it. In another way, it highlights psychiatric belatedness in this area.

Hofling (1955) says, "It is a matter of some curiosity when a group of therapeutic agents in widespread use over a long period of time is largely ignored in medical literature. That this has been the case with placebo is a matter of easy verification. A check of the most widely used textbooks of internal medicine, pharmacology, and therateutics reveals scarcely any reference to the subject, with nowhere so much as a page devoted to its general discussion."

Fisher (1956) says, although. "Placebo therapy is unique in its timeless potency and popularity . . . it has not achieved full scientific status. . . . Placebo therapy, the most common of all therapies, by paradox has a scanty literature with but few references. . . . The subject receives scant notice in textbooks on treatment, and is often ignored in lectures and courses on therapeutics."

Gliedman et al. (1957) comments, "In recent years, the results achieved by placebo have acquired a limited aura of respectability. The ability of inert compounds . . . to modify a variety of conditions . . . has begun to have a serious impact on medical thinking."

Trouton (1957) says. "Although numerous instances of the surprising efficacy of placebos in a wide variety of conditions have been reported lately, little has yet been done towards providing an explanation of the occurrence of placebo reactions, in terms of psychology." Kurland (1957) comments on the ". . . relatively unexplored areas" of the placebo effect and the paucity of information about this subject. [See also Charcot (1893), Freud (1948, 1950a), Janet (1924, 1925) and Jones (1923a) for similar thoughts on "suggestion."]

Recent interest in the placebo effect appears in psychology. Garner (1958) notes the ". . . seldom reported effects . . ." of the placebo, and says, "Much time and energy would be saved if research workers in this area were familiar with the many points of these papers before they undertook to explain the effect of drugs on patient behavior."

Factors responsible for recent psychiatric interest in the placebo effect

How can this situation be explained? The factors mentioned previously—being threatened, lack of knowledge, rigidity in thinking and disbelief in its importance—can be cited again. In addition, the closer relationship between psychiatrists and patients, with all the implications and consequences of transference and counter-transference phenomena, would make it more difficult for the latter to objectively evaluate such phenomena.

It is readily observed that the situation has changed in recent years. (Table 1, Figure 1). In addition to the factors mentioned previously—increased scientific knowledge, greater numbers of research personnel, concern with methodology, increased numbers of psychiatrists in research, etc.—several deserve special emphasis. In the last twenty-five years more therapeutic methods have been introduced into psychiatry than ever previously. Many of these methods—psychotherapy, ICT, ECT, rehabilitative (milieu) efforts, *lobotomy* and drugs—*appear* to be effective in as yet some unelucidated way. This should result in psychiatry being more secure and less threatened, and being able more readily to face scientific problems and criticize ineffective methods more objectively. The evaluation of these therapies raises many other problems. The complexity of evaluating contradictory reports, the difficulty of comparing different investigative methods, and the problem of isolating complex variables, inevitably leads, from many directions, to a consideration of the placebo and the placebo effect. It is perhaps not fortuitous that psychiatrists have become interested in the placebo effect following the introduction of the tranquilizing drugs in 1954. (Figure 1).

"Psychiatric" contributions to the study of the placebo effect

Despite psychiatrists' relatively recent concern with the placebo effect, they have contributed perhaps more substantially than all other previous groups of investigators. They have applied their special training and understanding with considerable fruitfulness.

Discussion of the placebo effect during the nineteenth century revolved around the concept of suggestion. This was stimulated by the advent of magnetic and hypnotic treatment. This development was not sudden and had historical roots in the past. As pointed out by Janet (1924, 1925), there was a long period of "Miraculous Healing" in which cure was attributed to Gods. A "Metaphysical Stage" followed in which power was invested in a particular person and exemplified by Mesmerism and Christian Science. The "Scientific Stage" (Bernheim, 1889; Janet, 1924, 1925) followed with the advent of hypnotism. These stages stamped their character on discussions of what is now called the placebo effect.

In the latter half of the 19th century many papers appeared on suggestion theory and therapy with particular emphasis on hypnosis. Hypnosis was viewed as the scientific attempt to investigate and use the principles of psychotherapy which had acted so blindly in the past (Bernheim, 1889; Janet, 1924, 1925). Suggestion was equated with hypnosis and hysteria and most of the papers used these terms as if they were synonymous (Bernheim, 1889; Breuer and Freud, 1957; Charcot, 1925; Ferenczi, 1950; Janet, 1924, 1925; Jones, 1923a, 1923b; Stekel, 1923). Although suggestion and hypnosis are related to the placebo effect and have many common principles, characteristics, and implications for each other, there is evidence (which will not be gone into at the present time) that these phenomena differ from one another in many details (e.g., conversion hysterics are poor placebo reactors, placebo effects can occur without direct, unconscious or conscious suggestions, etc.). For this reason, papers on hypnosis and suggestion per se, unless they have some importance for an understanding of the placebo effect, will not be summarized here (and are readily available elsewhere: Bernheim, 1889; Hull, 1933; Janet, 1925; Schilder, 1956; Weitzenhoffer, 1953).

Bernheim (1889) demonstrated with many appropriate examples the "suggestive" factors which led to ". . . the possible efficacy of various practices employed for the cure of disease and which have succeeded each other from ancient to modern times." His understanding of this phenomenon is based on his concept of hypnosis which is thought to be merely an extension or heightening of suggestion operating or present in every individual and involving all of human activity.

Similarly, Janet (1924, 1925), although critical of Bernheim's formulations about suggestibility and hypnosis, is well aware of the "suggestive" factors in the history of medical treatment. Janet criticizes the methodology of those attributing cures to miraculous, magical, religious and other suggestive forms of treatment. He cites the inadequacy of the diagnosis, records and statistical treatment, the poor definition of cure, evidence for cure and verification of the cures, and touches on the failure to formulate specificity, laws and indications for treatment. However, he is well aware that there is enough valid evidence for considering these treatments as truly effective and significant. He discusses the factors in the patient, physician and situation which are thought to underlie these successes: In the patient—enthusiasm, faith, belief, feelings in general, power of the imagination, expectant attention, faith in authority, the importance to the patient of being the object of investigation; in the physician—undoubting enthusiasm, faith, and belief, the unconscious personality of the healer; in the situation—the ritual, mystery and strangeness of the proceedings and the situation, changed environment, repetitive education, and suggestibility factors.

Freud (1950a) is in essential agreement with Janet that the majority of primitive treatments "must be classed under the head of psychotherapy," that this element centers into every therapeutic process, that all physicians use it, that it should be studied rather than used blindly, and that "a condition of expectant faith" was induced to effect cures. Concerning drugs Freud says, "It is not a modern dictum but an old saying of physicians that these diseases (psychoneuroses) are not cured by the drug but by the physician, that is by the personality of the physician, inasmuch as through it he exerts a mental influence." It is of interest that Freud viewed treatment in "hydropathic establishments" as effective, whereas today we would class such a cure as due to the placebo effect. Later, in 1912 and 1913, Freud (1949; 1950b; 1950c) emphasized the concept of transference, and made it the cornerstone for explaining the success of suggestive cures. Still later Freud (1948) says "Now that I once more approach the riddle of suggestion after having kept away from it for some 30 years, I find there is no change in the situation," and that it is necessary to formulate a concept of suggestion correctly and limit its extended use. He goes on, "But there has been no explanation of the nature of suggestion, that is, the conditions under which influence without logical foundation takes place."

Ferenczi, in 1909 (1950), holds that suggestion, hypnotism and healing of mental conflicts occurs "through repression, displacement and transference of disagreeable complexes," particularly transference of "repressed parental complexes" and of "unconscious libidinal impulses" onto the person of the suggestor, hypnotist, healer and physician.

Jones (1913; 1923a; 1923b) differentiates between two processes in suggestion—verbal and affective suggestion. The latter is more important and the basis for the former. "Affective suggestion" is the basis of therapeutic suggestion, and is "a rapport which depends on the transference of certain positive affective processes in the unconscious . . ." which are ". . . always components or derivatives of the psychosexual group of activities . . . one form of the more general mechanism of displacement, by means of which an affect is transferred from an original, unpleasant and repressed conception to another less acceptable one. . . . It acts by releasing the repressed desires that are finding expression in the form of symptoms, and allowing them to become attached to the idea of the physician, psychologically this means replacement of one symptom by another. . . ."

Hollingsworth (1912), a psychologist, following the lead of Rivers (1908), published a monograph on *The Influence of Caffein on Mental and Motor Efficiency*. Rivers is quoted approvingly and most of the latter's techniques are incorporated into the study.

Glover's (1931) paper on *The Therapeutic Effects of Inexact Interpretation*, although it does not discuss or mention the placebo, is concerned with the factors operating in successful suggestion from a psychoanalytic viewpoint and has many implications for an understanding of the placebo effect. The principle method is thought to be the increased effectiveness of repression, back by strong transference authority, the specific technique depending on the emphasis placed on various defensive mechanisms.

An excellent (practical and theoretical) discussion of "suggestion therapy" (which includes the placebo as one type of such therapy) appears in Levine's (1942) *Psychiatry and Medical Practice.* He discusses the ethics, indications, contraindications, dangers and theoretical factors from a psychoanalytic view. Diethelm (1936) briefly discusses the ethics of using placebos and comments on the suggestive influence of certain psychiatric treatments. As one of the participants in the 1946 Cornell Conference on Therapy, Diethelm (1946) comments on the little progress in understanding suggestibility (which includes the placebo effect) and stresses the belief on the part of the patient and the physician, and the physician's symbolic value and personality as important factors influencing suggestibility. At this same conference Wolff (1946) relates the placebo effect to his experiments on pain thresholds and to the pill being a potent symbol of the doctor which supports the patient in the former's absence. It symbolizes being cared for and gives emotional support or endorsement. It satisfies needs to feel dependent or may fulfill a need to be punished, and supports the desire to get well.

Appel et al. (1951) tabulate the results of psychotherapy with the neuroses and psychoses. They find it striking ". . . . that individual reports from various sources show little variation from the average improvement rate of 67 percent in the psychoneuroses and 39 percent in the schizophrenic illnesses," despite a wide variety of procedures which included reassurance at the one end of a continuum and psychoanalysis at the other end of the continuum. They discuss many of the variables that might have determined these results, and raise the question about the usefulness of psychotherapy which has not been adequately tested up to the present time. The paper does not mention the placebo effect specifically but considers many of its facets which would be called the placebo effect by other authors.

Hofling (1955), in an insightful article on the placebo effect for general practitioners, widens the concept of the placebo by defining it as, "A therapeutic measure which is administered largely or entirely for a psychologic effect not inherent in its physical or pharmacologic properties." He goes on to discuss the factors influencing the effectiveness, the therapeutic indications and the ethics of placebos. His elucidation of the attitudes and feelings ("counter-transference phenomena") that accompany, result in or result from the prescribing of placebos is of considerable interest and a major contribution to the understanding of the placebo effect. These factors, rarely considered previously, are shown to influence the effectiveness of and the attitudes toward the placebo. This aspect has been the special and unique contribution of psychiatry and has been considered by others in addition (Clyne, 1953; Whitehorn, 1958).

Abramson, Jarvik, Levine, Kaufman, and Hirsch (1955) discuss the placebo effect as related to LSD, enumerate important variables in such studies, list some of the characteristics of placebo reactors, and correlate the placebo effect with responses to the Cornell Medical Index Health Questionnaire, arithmetic test, Rorschach, and the Wechsler-Bellevue Intelligence Scale.

Fisher and Olin (1956) in a clinical study of patients receiving medication with potent autonomic properties (including a placebo in a double blind study), discuss the dynamics of placebo therapy. A broad definition of the placebo is offered, "A placebo may be any object offered with therapeutic intent," and adds that, "The 'placebo reaction' occurs in psychotherapy even without a pill, in the so-called 'transference' cure." Traits of the positive and negative placebo reactor stemming from this study are delineated.

Tibbetts and Hawkins (1956) cite their experiments with physical treatments in psychiatry and relate their findings to the placebo effect. Traits found to characterize the positive placebo reactor are listed. Baker and Thorpe (1957) conducted a clinical study in which a placebo control resulted in significantly greater improvement than a tranquilizer. They list several of the methodological variables of importance in understanding the placebo effect which were felt to be responsible for this astonishing outcome. Trouton (1957) reviews the literature and relates the placebo effect to learning and personality theories. Hoffer (1956) comments on ". . . . the psychologic or placebo factors that no longer can be ignored." He lists three psychological factors that must be considered when drugs are studied, and cites his experiences with LSD in this regard.

Psychodynamic and conditional reflex actions of placebos are discussed by Kurland (1957) who offers some tentative conclusions resulting from a study now in progress.

A number of excellent papers on the placebo effect have emanated from a group at the Johns Hopkins Medical School. Psychotherapy and the placebo effect is discussed by Rosenthal and Frank (1956). They review the literature and demonstrate the importance of considering this factor in research and evaluation of psychotherapy. Gliedman et al. (1957) summarize some conditional research studies on dogs and relate placebo reactivity to established learning concepts. Gliedman et al. (1958) elaborate further on the placebo effect in the context of a study comparing short-term psychotherapy with a placebo. Both procedures resulted in similar "symptom reduction" which was not significantly different from one another. They relate the nature of the symptoms relieved to Beecher's concept of the "reaction component of suffering." Although they comment on the limitations of their study, and many others could be raised, it does represent an attempt to study experimentally the effect of the placebo in the very complicated and difficult area of psychotherapy. Whitehorn, in a recent article (1958), defines the placebo effect as, " . . . . all those psychological and psychophysiological benefits or determinants which quite directly involve the patient's expectations and depend directly upon the diminution or augmentation of the patient's apprehension by the symbolism of medication or the symbolic implications of the physician's behavior and attitudes." This definition adds a dynamic dimension to the usual definition—the expectation and apprehension of the patient. This succinct and insightful article touches on most of the major questions about the placebo effect—theory, psychotherapy, ethics, double blind studies, the doctor-patient relationship, psychodynamics, and the importance of research on this subject. (See also Frank et al., 1957; Imber et al., 1957).

Many of the above articles review the literature on the placebo. Substantial contributions to methodological problems, which involve the use of placebos and indirect concern with the placebo effect, are appearing in increasing numbers by psychiatrists (Feldman, 1956; Horwitt, 1956; Sabshin and Ramot, 1956; Sainz, Biegelow, & Barwise, 1957; Smith & Wittson, 1957; Rashkis & Smarr, 1957a; 1957b).

In 1956 a three day "Conference on the Evaluation of Pharmacotherapy in Mental Illness" was sponsored by the National Academy of Sciences (1956) and should be published in the near future.

DISCUSSION

The placebo effect appears to consist of three factors which are distinct from one another but which are often used interchangeably in the literature.

The first involves methodological errors resulting from variables other than the experimental variable determining results. These errors can arise at any and all stages of an experiment. If the experimental group is not compared with a control group which has been matched, randomized or analyzed for age, sex, acuteness or chronicity of illness, length of hospitalization, diagnosis, prognosis, psychodynamic factors, nutritional and physiological states and a great number of other variables, the experimental results are very likely to be erroneous. These controls aid in minimizing the omnipresent positive or negative bias of investigators and observers. The effect of spontaneous remission during the course of illness must be considered in the evaluation of therapeutic efficacy. The increasing use of the double blind proceure (Shapiro, Dussik, Tolentino, & Azekoff, 1959) reflects the concern of investigators with these problems.

Studies planned with diligence in every respect, including the use of the double blind procedure, can result in a placebo appearing significantly superior to a tranquilizing drug if the placebo is sweet and the tranquilizer bitter; and if the placebo can be dissolved or easily distinguished from the active drug, the results may reflect, not the effect of medication, but the attitudes of the personnel administering and evaluating the drug (Baker & Thorpe, 1957). The effect of the observer's attitude determining results with tranquilizing drugs has also been demonstrated graphically by Feldman (1956) who found that the reported therapeutic effect of chlorpromazine correlated closely with the physician's attitude to the drug. Many other such examples could be cited.

After examination of the experimental evidence, as well as a consideration of the history of medicine, the literature on the placebo effect, suggestibility, etc., another factor appears which may be a variable but which is different from the usual methodological variables. If all the known and possible variables are controlled or excluded except for this one the results are very likely to be in error. This factor is the placebo effect, the effect of th doctor himself (or some symbolic representative of the doctor) as therapeutic agent (Freud, 1950a; Findley, 1953; Houston, 1938), the most widely used of all agents (Balint, 1955; Cornell Conference, 1946; Fisher & Olin, 1956; Janet, 1924; Jones, 1923a).

This factor assumes special importance because it has dynamic therapeutic effects which are different from simple variables such as age and chronicity of illness. The powerful therapeutic potential of the placebo effect should be further investigated so that its mechanism is understood and its possible uses explored. It may help elucidate some of the problems in psychotherapy and liberate for further inquiry the effects of psychotherapy which appear to be above and beyond the mere result of the placebo effect. The principle(s) underlying the effect of this variable can be extended to non-therapeutic experimental situations which involve an interpersonal relationship with an investigator, or even some symbolic representative of the latter. The effect of the observer or investigator in experimentation requires further exploration.

A third factor is the effect of the placebo when it is an uncontrolled variable in experimental research or therapeutic evaluation which then becomes subject to the methodological errors described previously.

Thus, a clarification of the placebo effect requires that a distinction be made between methodological variables, the placebo effect itself, and the placebo effect as an uncontrolled variable. In addition, as correctly pointed out by Fisher (1956), the placebo should be distinguished from the placebo effect, the placebo being the agent which may or may not result in a placebo effect.

These considerations have important implications for psychiatry. It should stimulate the development of the sensitive methodology required by the complex factors in psychiatry. The perennial misevaluation of new therapies may be avoided or limited. The recent flood of newly introduced therapeutic agents and procedures demands reliable evaluation. It is important to tease out the effects due to specific factors and those due to experimental variables and the placebo effect. It is important to determine whether, to what extent, and why a specific therapy may require a placebo effect to be successful, neither possibly being effective separately but only in combination. As pointed out by Rosenthal and Frank (1956), the effects of psychotherapy may be obscured by under or overevaluation because some patients may respond without therapy, some to any kind, and others only to specific therapy. The effect of the "social milieu" or "psychosocial environment" should be clarified and distinguished from the placebo effect if possible, if it is distinguishable in fact, and not itself a product of the placebo effect (Greenblatt, Levinson, & Shapiro, 1959).

Occasional records of ancient medicine having stumbled upon a useful drug do occur. The inability, however, to scientifically evaluate the specific usefulness of the drug usually resulted in its loss to future generations. The ancient Chinese gave ground-up "dragon bones" to children with convulsions the calcium being effective for infantile tetany (Haggard, 1933). Burnt sponge, which contains iodine, was used to treat simple goiter (Haggard, 1933). Withering used his digitalis concoction (Fox-glove) for all cases of dropsey, which was regarded as a primary disease (Garrison, 1921; Major, 1955). The recognition that digitalis had a beneficial effect in only certain types of dropsey, that caused by congestive heart failure, and that it was ineffective in renal disease, vitamin deficiency, hypothyroidsim, cirrhosis, adrenal malfunction, neopalsm, etc., led to the former's more effective treatment and to advances in the understanding and treatment of the other conditions. Sydenham in the 17th century is credited with a major contribution to the end of "galenicals" in medicine, and the beginnings of scientific medicine, by demonstrating the specificity of cinchoma bark for fever of malarial origin (Garrison, 1921; Haggard, 1929; Haggard, 1934; Major, 1954; Major, 1955; Pepper, 1945).

Although psychiatry is on a much higher level than medicine of that period there are some rough similarities that do not require elaboration.

This paper is not meant to derogate the ingenuity, inventiveness, sensitivity, and value of the individual clinician. The past, present, and future would be bleak indeed if their creative function were superseded by a mechanistic methodology. Scientific methodology rarely if ever creates ideas in itself but is used to test these ideas and concepts. But it is also necessary to recognize the limitations and dangers inherent in the "common sense" method of the clinician. This has been demonstrated clearly in the case of morphine. After all the centuries it has been used, the dosage arrived at in this country is 50 to 100 per cent greater than the one that gives essentially the maximum of pain relief, as determined by careful methodological evaluation. (Beecher, 1952; Denton and Beecher, 1949; Lasagna and Beecher, 1954; Lasagna et al., 1954; Keats, Beecher, & Mosteller, 1950; Lee, 1942). It does not follow, however, that recognition be denied the astute clinician who first used morphine, or those who rediscovered it in other places and at other times, or those who followed reifying its usefulness. Their importance and function is gainsaid. Our concern is with minimizing the errors of the astute clinician and the hyperbole of the less gifted, and with the adding of clarity, objectivity, reliability and sensitivity to the "common sense" and at times the "uncommon sense" of the clinician. This requires concern with methodological problems in general and the placebo effect as a methodological problem in particular. Finally the recognition of the placebo effect, an important variable in methodology, capable of potent and extensive, therapeutic effects, requires special attention .

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[From British Medical Journal, Apr. 10, 1965]

INDOMETHACIN AND PEPTIC ULCER

SIR,—Last year we reported a high incidence of peptic ulcers (5 out of 18 patients) in patients with rheumatic diseases treated with indomethacin (11 January 1964, p. 118). Since September 1963 we have used only capsules of indomethacin, and we now wish to report a much-lessened incidence of gastrointestinal side-effects.

"Fourteen patients with a variety of rheumatic diseases were treated for periods varying from one to 17 months with capsules containing indomethacin, 25 mg., thrice daily with food. All patients had a barium-meal examination before the treatment and at least once during the period of treatment. Three patients who gave a history of peptic ulcer received concomitant anticholinergic-drug therapy and antacids.

"One patient died during the course of treatment from cerebral haemorrhage, but at necropsy there was no ulceration of the gastro-intestinal tract. One of the patients with a past history of peptic ulcer developed a gastric ulcer; indomethacin was discontinued and the occult-blood test became negative. The second patient with a history of peptic ulcer who had developed ulceration with indomethacin tablets did not develop an ulcer when given indomethacin capsules. The third patient with a peptic ulcer history did not develop ulceration, either on tablets or on capsules."

Thus the incidence of peptic ulceration can be reduced by switching from tablets to capsules. Moreover, other side-effects such as vertigo, headache, nausea—which were relatively common in patients treated by tablets—did not occur. In our previous report we suggested that a lower dosage of indomethacin would overcome troublesome side-effects, and we feel that this has been achieved without any reduction of anti-rheumatic efficacy.—We are, etc.,

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[From British Medical Journal, May 1, 1965]

INDOMETHACIN AND PEPTIC ULCER

SIR,—Dr. Olle Lövgren and Dr. Erik Allander (10 April, p. 996) must indeed have been fortunate to have found such a low incidence of side-effects from capsules of indomethacin. In my own experience, headache, vertigo, or nausea occurs in at least 50% of patients receiving this drug, even with the modest dosage of 25 mg. thrice daily. In addition, two of my patients have developed an acute toxic psychosis which was almost certainly due to indomethacin.

Apart from these unpleasant side-effects, I have not so far observed anything to suggest that this drug has an "anti-rheumatic effect"—whatever that may mean. In my experience, it appears to have only an analgesic effect, and this in a minority of patients suffering from rheumatoid or osteoarthritis, and is much inferior in its effect to phenylbutazone in this group of diseases.—I am, etc.,

A. C. BOYLE, M.D.

London W.1.

[From British Medical Journal, May 22, 1965]

INDOMETHACIN: STUDIES OF ABSORPTION AND OF THE USE OF INDOMETHACIN SUPPOSITORIES

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[*Brit. med. J.*, 1965, 1, 1354–1356]

Indomethacin, a new drug for treating arthritic disorders, was introduced for clinical trial in 1962. It is chemically unrelated to either corticosteroids or other anti-inflammatory compounds, and has an indole structure within its formula [1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid].

Although anti-inflammatory activity can be demonstrated in animals (Winter, Risley, and Nuss, 1963), this effect has not been conclusively shown in man, though measurable reduction in the finger-swellings of patients with rheumatoid arthritis, as measured by jeweller's rings, occurs (Hart and Boardman, 1963). Other parameters of inflammation such as the erythrocyte sedimentation rate are unaffected.

The reports of controlled clinical trials (Hart and Boardman, 1963; Wanka Jones, Wood, and Dixon, 1964; Percy, Stephenson, and Thompson, 1964) prove that this drug relieves symptoms in different arthritic disorders such as rheumatoid arthritis, osteoarthrosis, ankylosing spondylitis, and gout. Unfortunately, like other analgesic and anti-inflammatory agents, it carrier the risk of gastro-intestinal irritation. The tablets which were used originally led to peptic ulceration in some patients (Catoggio, Centurion, Alberti, Roldan, and Canepa, 1964; Kelly, 1964; Lövgren and Allander, 1964; Robinson, 1964 Wanka *et al.*, 1964), and anorexia, nausea, vomting, dyspepsia, and diarrhoea have also occurred. Other side-effects have involved the central nervous system (headache, giddiness, faintness, mental changes, drowsiness, and blurring of vision).

The introduction of gelatin capsules containing powdered indomethacin and the prescribing of smaller doses have led to a decreased incidence of side-effects. However, we thought it important to assess its absorption from the rectum in the hope that suppositories could be used for patients suffering from peptic ulcers, for those who develop gastric intolerance to the drug, and for patients who require larger doses than can safely be given by mouth.

MATERIALS AND METHODS

Of 40 patients studied, 34 suffered from rheumatoid arthritis, 3 from osteoarthrosis, 2 from ankylosing spondylitis, and 1 from gout. Many were severely ill or resistant to other drugs, or had developed complications of corticosteroid therapy.

The average dose of indomethacin, as capsules, is 25 mg. four times a day. It was decided to compare initially the serum levels and clinical response after giving 100 mg. either as a single oral dose or as a suppository in 10 patients. The capsules or suppositories were given one-half to one-and-a-half hours after a normal breakfast.

Estimation of Indomethacin

The following reagents were used.

1. *Heptane* was washed successively with N NaOh, N HCl, and distilled water *in this order*, and passed through filterpaper to remove residual water.

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2. *Citrate buffers* (*p*H 5): Strength (1) molar (citric acid 210 g., NaOH 90 g., H_2O to 1,000 ml.). (2) 0.2 molar.

3. *Phosphate buffer* (*p*H 8: Disodium hydrogen phosphate $Na_2HPO_4 2H_2O$), 16.9g.; potassium dihydrogen phosphate (KH_2PO_4), 0.68 g.; water to 1,000 ml.

4. *Stock solution indomethacin* (*25μg./ml.*). Indomethacin 25 mg. was dissolved in 1,000 ml. of the phosphate buffer. This required continuous stirring for four to five hours and standing for 24 hours at 4° C before use.

The following method of estimating indomethacin in the serum, modified from that of the manufacturers, was used. One millilitre of serum was pipetted into a glass-stoppered centrifuge-tube containing 2 ml. of *M* citrate buffer (*p*H 5) and 25 ml. of heptane containing 5% isoamyl alcohol. The contents of the tube were mechanically shaken for 15 minutes and then centrifuged. Twenty millilitres of the upper heptane phase was pipetted into a second centrifuge-tube containing 5 ml. of 0.2 *M* citrate buffer (*p*H 5). This was shaken for a few minutes and then centrifuged. Ten millilitres of the heptane phase was pipetted into a third centrifuge-tube containing 3 ml. of 0.1 *N* NaOH and shaken for five minutes. After centrifuging, the lower aqueous phase was aspirated into a quartz cuvette and read in an Aminco-Bowman spectrophotofluorometer (activation about 300 mμ, fluorescence about 385 mμ, the exact peaks for each individual machine being found by scanning). Standards were set up by diluting the stock indomethacin solution with distilled water and adding this to normal serum to give concentrations of 0, 2.5, and 5 μg. of indomethacin per ml. These sera can be kept by deep-freezing, but the stock indomethacin solution deteriorates. The graph of concentration against fluorescent reading was linear, and only three points were necessary to form each calibrating graph.

The method is not difficult and is both accurate and precise, provided care is paid to details; for example, traces of alkali remaining from routine laboratory washing procedures may interfere. Indomethacin is light-sensitive, so that prolonged exposure to daylight or delay in taking readings in the spectrophotofluorometer must be avoided. Erroneous results occurred if the patient was taking aspirin, for salicylates are also extracted by this technique and fluoresce at a similar wavelength; paracetamol does not interfere. The accuracy is shown in Fig. 1, where aliquots were randomized and then estimated serially.

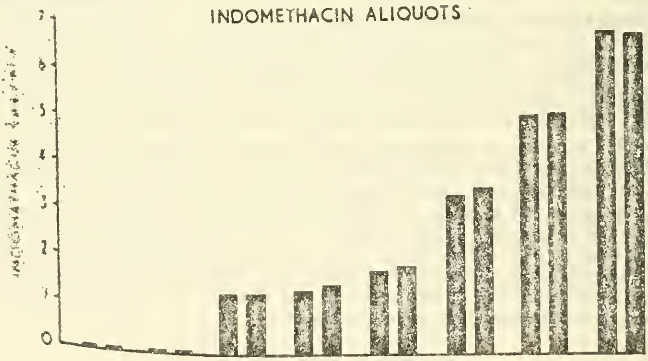

FIGURE 1.—Serum indomethacin levels in unknown paired aliquots.

The distribution of paired samples of a homo-scedastic nature, and thus the percentage error will be relatively greater when estimating lower concentrations of indomethacin. A single reading has a 95% chance of being within 0.1 μg. of the true value.

The clinical effectiveness in all 40 patients was assessed by relief of pain, improvement of function, and by the cuff dolorimeter, a device for measuring tenderness of the finger-joints (to be published): as well as by the reduction of other therapy such as corticosteroids. No patient was considered to have responded to indomethacin unless relapse took place when dummy capsules or suppositories were substituted without the patient's knowledge.

RESULTS

Indomethacin was absorbed satisfactorily from the rectum. The peak levels obtained varied widely between individuals, being 1.1–3.5 µg./ml. (mean of 10 cases, 2.15 µg./ml.) after 100 mg. of indomethacin by rectum and 1.4–6.2 µg./ml. (mean of 10 cases, 2.85 µg./ml.) after 100 mg. orally. It will be seen (Fig. 2) that the serum level in the average case after 100 mg. by rectum was 75% of that when given by mouth.

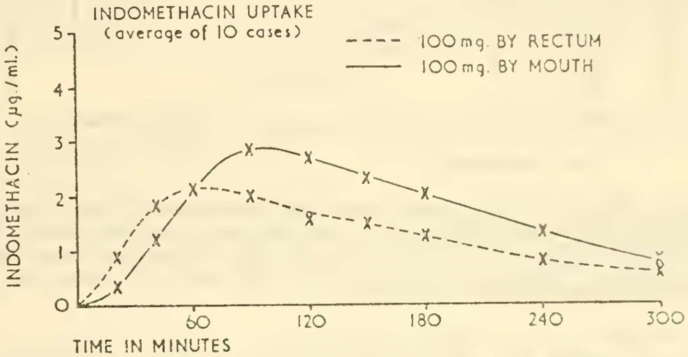

FIGURE 2.—Average serum levels obtained after giving indomethacin by mouth and by rectum.

Absorption invariably started shortly after a suppository, though it was delayed to a varying extent, up to two hours, after the capsules (Fig. 3); indeed, in five patients it had not begun at 20 minutes. Symptomatic relief showed a similar pattern to the serum levels, starting 20 to 30 minutes after a suppository and 40 to 60 minutes after oral administration (Fig. 4). A curious and unexplained finding was the duration of relief of pain from a suppository in some patients. When 100 mg. was given last thing at night, not only was early-morning stiffness relieved but pain was lessened until midday, up to 16 hours. Proof when relying on subjective phenomena is always difficult. No such difficulty was found with placebo suppositories; indeed, the relapse was usually obvious next morning.

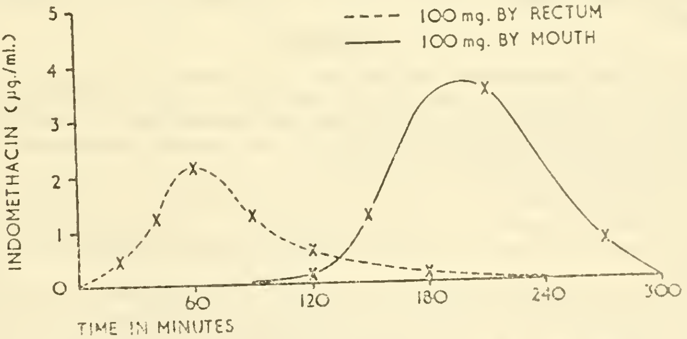

FIGURE 3.—Results in a woman aged 49, showing that absorption may be delayed up to two hours after oral administration.

There was no practical difficulty in insertion of the suppositories except in patients with severe deformity of the hands, when a nurse or relative could do this instead. Patients preferred to use the suppositories at night, as they were

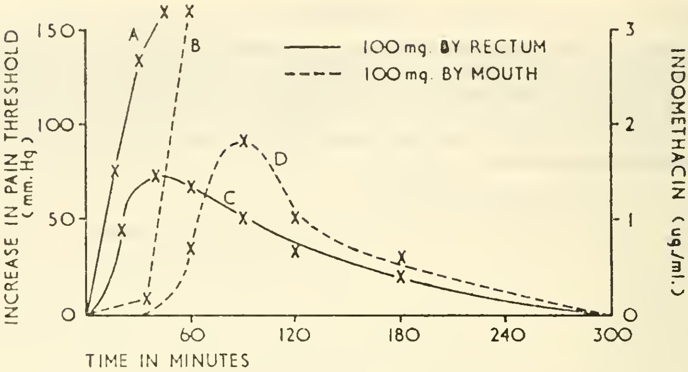

FIGURE 4.—Effect of indomethacin upon joint tenderness as shown by the cuff dolorimeter. B shows the decrease in tenderness of a proximal interphalangeal joint after 100 mg. by mouth, the corresponding serum level being shown in D. A. shows the decrease in tenderness of the same joint after 100 mg. by rectum, the serum level being shown in C.

easily retained and were unaffected by defecation, which is usually a morning habit. Local effects from the suppositories were noted in three cases. Sigmoidoscopy was performed in 10 patients, and the rectal mucosa was normal. Occult blood tests on the stools, performed routinely, showed no evidence of bleeding.

No dyspeptic symptoms occurred when suppositories were used, and systemic side-effects such as headaches or dizziness were negligible.

Thirty (75%) of the 40 patients given suppositories obtained a good result, and the clinical effects were similar whether the drug was given by mouth or by rectum. Certain patients who failed to respond to a daily dosage of 100 to 150 mg. were given larger doses, up to 300 mg. daily, by supplementing the oral doses with suppositories. This procedure might be effective, though it was more likely to produce side-effects.

Isolated serum levels were found to be of no practical value in controlling treatment. The peak serum level after rectal administration closely corresponded to one hour, though after oral administration it was too variable to be predictable. The maximum serum levels obtained in different patients did not equate with the degree of relief of pain or the severity of side-effects in these patients.

DISCUSSION

This trial has shown that indomethacin is a valuable drug for the treatment of patients with various types of arthritis. Relapse when a dummy tablet or suppository is substituted is striking and sometimes suggests a "rebound effect." Its use may enable corticosteroid therapy to be reduced in some patients and occasionally to be discontinued altogether.

Capsules are suitable for routine use, although suppositories can be prescribed for the following reasons: (1) when oral administration is contraindicated because of dyspepsia or peptic ulceration, and (2) to increase the total daily dosage above limits now regarded as safe when given by mouth (such as 150 mg. daily).

Side-effects have been no more than an inconvenience, and in particular, no gastric disturbance has occurred in our trial. It is not yet known why oral indomethacin, like other analgesic or anti-inflammatory drugs, may injure the stomach. If the disturbance is due solely to local damage to the mucous, it should be avoided by rectal administration. If, however, indomethacin causes an increase in the hydrochloric-acid secretion or a decrease in mucosal resistance from a systemic action, there may still be a risk of this after suppositories.

SUMMARY

The estimation of serum levels of indomethacin has shown that it is absorbed satisfactorily from the rectum.

Suppositories containing this drug can be used when capsules are contraindicated because of peptic ulcer or to supplement the total daily dosage.

Indomethacin is a valuable drug for the treatment of patients with various types of arthritis.

We are grateful for the help afforded us by our colleagues in particular Dr. T. P. Whitehead and Dr. N. Crawford; also Mr. T. F. Dee, who helped with the preparation of the diagrams. Dr. R. Hodgkinson, of Merck Sharp and Dohme Ltd., kindly arranged for our supplies of indomethacin.

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[Leading Articles]

[From British Medical Journal, May 22, 1965]

INDOMETHACIN

After two years of clinical trial indomethacin is now generally available under the Health Service. Early publications[1] showed that it had analgesic and anti-inflammatory properties which were not medicated via the pituitary or adrenal. The first trials[2–7] reported that side-effects were common, particularly headaches and dizziness. Gastrointestinal side-effects, noted in all experimental animals used, also occurred in man, though less frequently, but reports of serious and occasional fatal complications were made comparatively early.[8 9] The incidence of side-effects dropped as soon as capsules were substituted for tablets[10] and the dosage was reduced from 300 mg. to 75–100 mg. daily. But unpleasant reactions are still the main reason for therapy to be discontinued: they appear in about a quarter to a third of all patients on the drug. A review of its properties has also appeared in this journal.[11] Most workers find that acute gout usually responds rapidly to treatment with indomethacin, and, as P. L. Boardman and F. Dudley Hart point out,[12] rapidity of action is an important asset in any drug used for treating this agonizing disorder. Patients with ankylosing spondylitis also frequently benefit—both those with early disease and those with more advanced apparently "burnt out" disease who still suffer pain. While some patients with spondylitis intolerant of phenylbutazone because of gastrointestinal side-effects do well on indomethacin, others cannot tolerate it, usually because of headaches and dizziness; in a few cases dyspepsia develops with both drugs. We have, therefore, in indomethacin another drug among the not very many which are available for the treatment of this condition. The same applies to osteoarthritis of the hip, some patients responding better to one substance, some to the other. In a double-blind controlled study by J. Wanka and A. St. J. Dixon [13] indomethacin proved to be superior to placebo. In rheumatoid arthritis the drug has also proved helpful, though slightly less so than in ankylosing spondylitis and osteoarthritis.

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[11] *Brit. med. J.*, 1964, 2, 429.

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In the B.M.J. this week Drs. L. P. J. Holt and C. F. Hawkins report at page 1354 on its effectiveness when given at night by suppository. It was found to relieve the morning stiffness which is so unpleasant a feature of active rehumatoid arthritis, clinical improvement in some cases lasting until mid-day, up to 16 hours after administration of the drug. The same effect on morning stiffness can be obtained in some cases by giving 25–50 mg. by mouth late at night after food, and it seems that this form of therapy can be an alternative to small evening doses of corticosteroids given for the same purpose. Holt and Hawkins noted no dyspeptic side-effects in their 40 patients given suppositories, and improvement was seen in 30 of them. Absorption by this route was clearly effective as judged by blood levels of the drug and by clinical assessment. Nevertheless, if experience with this drug parallels that with phenylbutazone given by suppository, dyspepsia may yet be noted in some cases, particularly if dosage is increased.

Apart from dyspepsia indomethacin may occasionally cause insidious loss of blood—and consequently anaemia—without gastro-intestinal symptoms. Studies using erythrocytes labelled with radioactive chromate [9] have shown a loss averaging 1.2 ml. daily in 6 out of 12 subjects, all of whom on aspirin lost considerably more (an average of 5.9 ml. daily). It seems that almost all drugs which help the rheumatic sufferer may also irritate the gastro-intestinal tract. While indomethacin is no exception, most patients tolerate it well, and dyspepsia is a less common complaint than headaches and a variety of cerebral sensations which are not serious and which rapidly abate on reducing or stopping dosage. Further toxic effects may be seen now that the drug is generally released—and it is important that their notification should be prompt. But it seems that the analgesic and anti-inflammatory properties of indomethacin may prove helpful in the treatment of many of the rheumatic disorders.

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[13] Wanka, J., and Dixon, A. St. J., *Ann. rheum. Dis.*, 1964, 23, 288.

[Correspondence]

[From British Medical Journal, Aug. 14, 1965]

INDOMETHACIN SUPPOSITORIES FOR ARTHRITIS

SIR,—With regard to the article by Dr. L. P. J. Holt and Dr. C. F. Hawkins (22 May, p. 1354), we have recently used indomethacin suppositories in 11 patients. Nine of these had gastric intolerance to anti-inflammatory drugs by mouth, gastric ulcers being demonstrated by barium meal in two cases. A dose of 100 mg. at noon and 100 mg. at night was found to be most effective. In all cases proctoscopy showed normal rectal mucosa, a finding noted by the authors.

Seven of our patients had rheumatoid arthritis, and five of these made a good response without side-effects. One of this group complained of giddiness, which was relieved by halving the dose given in suppository form while maintaining the same amount of symptomatic relief. In one case where no improvement was made on indomethacin by mouth therapeutic response was obtained by the suppository form. In two further cases of rheumatoid arthritis indomethacin capsules were given in a dose of 25 mg., three times a day, together with a 100-mg. suppository at night. Considerable relief of morning stiffness occurred.

Two cases of acute gout with severe dyspepsia obtained relief within 48 hours while on indomethacin suppositories—in one case twice daily and in the other three a day—without side-effects.

We endorse the findings of Dr. Holt and Dr. Hawkins that indomethacin suppositories are of use in gaining relief from arthritis where capsules are contraindicated, or to supplement total daily dosage. It is particularly useful when morning stiffness is the dominant symptom.—We are, etc.,

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[From British Medical Journal, Oct. 23, 1965]

INDOMETHACIN AND GASTRIC ULCER

SIR,—Now that indomethacin has been generally released as a useful drug in a number of the rheumatic disorders it is as well to appreciate that not only may silent bleeding occur from the intestinal tract—so that patients without dyspeptic symptoms may develop a gradual and insidious anaema from blood loss—but also large gastric ulcers may appear, also without dyspetic symptoms, which are often looked upon as possibly or probably malignant from their radiological appearance and the insidious nature of their appearance. I have now seen three such cases, in all of which healing occurred on discontinuing the drug or on transferring to suppositories of the same substance.

Though headaches or a variety of cerebral sensations may occur with indomethacin, these are usually related to dose and disappear rapidly on reduction or stopping of the drug. Dyspepsia or development of the silent ulcer may occur at any time, apparently on any dosage, not necessarily a high one. Though gastro-intestinal, as opposed to cerebral, side-effects are rare they are much more serious. When surgery is contemplated in addition, as it may be with the pseudo-malignant gastric ulcer if its true nature is not appreciated, the risk increases further, Many, if not most, of the serious gastro-intestinal side-effects reported to date have been in patients receiving corticosteroids as well as indomethacin. The three cases referred to here were on indomethacin only.—I am, etc.

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[From Journal of the American Medical Association, Nov. 8, 1965, Vol. 194, No. 6]

CONTROL OF FEVER IN HODGKIN'S DISEASE BY INDOMETHACIN*

(By Harold R. Silberman, M.D., Thomas G. McGinn, M.D., and
William B. Kremer, M.D.)

Indomethacin (Indocin), a new nonsteroid, anti-inflammatory, antipyretic agent, was evaluated in nine patients with fever due to Hodgkin's disease. Each patient had significant and prolonged fever despite treatment by cytotoxic chemotherapy, salicylates, and corticosteroids. In all instances, prompt and continuous suppression of fever was achieved without untoward effects. The course of the disease in these cases was not apparently altered. This agent could be a useful adjunct in the symptomatic treatment of fever in Hodgkin's disease.

Fever, without obvious infection, has been recognized for many years as a cardinal symptom of Hodgkin's disease.[1] It is present in 30% to 60% of patients as part of the initial manifestation of this illness.[2 3 4] The fever may be distinctive as with the relapsing form of fever, described by Pel[5] and Ebstein,[6] characterized by periods of pyrexia alternating with intervals during which the temperature is normal or subnormal. More commonly the fever is "typeless,"[7] being continuous, remittent, intermittent, or occurring in combinations. It is of interest that the presence of fever usually means active occult disease, although it can be independent of both the extent of disease and the duration of the illness.[4 8] Indeed, at times patients seem to respond satisfactorily to cytotoxic agents, with obvious lymph node or organ regression, while fever persists.[2 9]

The disability directly attributable to fever can be quite significant with the sequelae of malaise, weakness, chills, sweating, and anorexia. Many attempts have been made to suppress the fever when it is unresponsive to specific tumor chemotherapy. Aspiring is widely used as an antipyretic agent in these instances, but in one carefull studied series only four of 35 patients had defervescence.[9] Both aminopyrine[9] and phenylbutazone have been used successfully as antipyretic agents in this setting, but the incidence of toxicity, particularly of the latter compound, limits their widespread use.

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*From the Hematology Laboratory, Duke Hospital, and the Department of Medicine, Duke University School of Medicine, Durham, N.C.

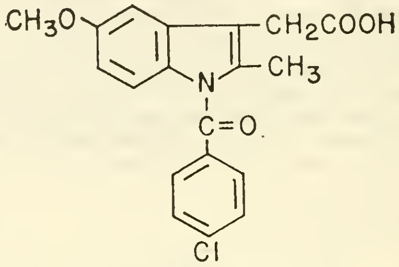
Reprint requests to Duke Hospital, Durham, N.C. (Dr. Silberman).

NOTE.—Footnotes at end of article, p. 3039, infra.

The prompt lysis of fever in a patient with lupus erythematosis treated with a new anti-inflammatory compound, indomethacin (Indocin), suggested a trial in the fever of Hodgkin's disease.

PHARMACOLOGY

The preclinical and clinical data show that indomethacin (1-[chlorobenzoyl]-5-methoxy,2-methylindole-35-acetic acid) (Fig. 1) is a structurally new and potent antipyretic agent with a low incidence of side effects. This nonsteroidal compound inhibits the fever produced by injection of a bacterial lipopolysaccharide, *Escherichia coli endotoxin*, in both rabbits and rats.[10] It appears to be more potent in this respect than aspirin, aminopyrine, or phenylbutazone.[10] The drug is well absorbed after oral administration in various species, including man.[11] After 150 mg of indomethacin is given orally, the greatest plasma concentration is reached in four hours.[11] From the peak value at four hours the regression line of plasma values in man shows a half-life of two hours.[11] The drug is rapidly excreted with about two thirds of a given dose appearing in the urine as indomethacin glucurouide and the rest as free indomethacin in the feces.[11,12] In in harmful effects.[13,14,15,16] Studies of hematological, renal, and hepatic func- a therapeutic dose has been related to alterations in the gastrointestinal tract.[11]



INDOMETHACIN

FIGURE 1.—Chemical structure of indomethacin (1-[p-chlorobenzoyl]-5-methoxy, 2-methylindole-3-acetic acid).

During the past few years the drug has undergone extensive clinical trial in patients with inflammatory joint disease including rheumatoid arthritis and acute gout. Maintained drug administration for as long as two years has not resulted in harmful effects.[13,14,15,16] Studies of hematological, renal, and hepatic functions before, during, and after drug administration failed to reveal any significant derangement.[13,16] Minor side effects such as dizziness, headache, dyspepsia, nausea, and vomiting were encountered but usually could be eliminated by decreasing the dosage.[13,15,17,19] Rarely, indomethacin seemed to be related to the appearance of peptic ulcer.[19,20]

PATIENT SELECTION

Nine patients with Hodgkin's disease having severe, refractory fever were selected between May 1963 and January 1965 to evaluate this new antipyretic. Disease duration ranged from 1 to 13 years and the extent of disease varied considerably (Table). Satisfactory control of disease and fever was not achieved by intensive therapy with cytotoxic agents, adrenal corticosteroids, or aspirin. The best combination of drugs for each individual was continued and indomethacin was added.

Pretrial studies included clinical evaluation, complete blood counts, and renal and hepatic function studies. The presence of a significant complicating bacterial or fungal infection was considered in each patient and ruled out as well as possible by appropriate studies.

The initial dose of indomethacin varied from 25 to 50 mg every 6 to 8 hours. During the early period of therapy all patients were hospitalized and rectal temperatures recorded every four hours. Hematological studies were done twice a week and other appropriate laboratory studies were repeated biweekly. Measurements of objective disease parameters were continued.

Summary of Fever Responses in Patient With Hodgkin's Disease Treated With Indomethacin

Patient No. Age/Sex	Disease Duration, Yr	Clinical Features	Prior Therapy	Present Agents	Response of Fever	Indomethacin Dosage		Therapeutic Results
						Dose	Period	
F40196 42/F	6	Anemia, cervical and axillary adenopathy, hepatomegaly, Herpes zoster, remittent fever of 100.4-104 F (38-40 C)	melphalan, prednisone, mechlorethamine hydrochloride vincristine sulfate, chlorambucil, fluoxymesterone	mechlorethamine HCl, prednisone, fluoxymesterone, tetracycline, kanamycin sulfate	None None None None None	25 mg 4 × daily 25 mg 3 × daily	48 hr 2 mo	Complete defervescence within 8 hr and continued afebrile until death
G10253 34/M	3	Sweats, axillary adenopathy, fever, anemia, abnormal marrow, remittent fever of 100.4-102.2 F (38-39 C)	x-ray, mechlorethamine HCl, methylprednisolone	methylprednisolone, mechlorethamine HCl	None None	25 mg/ 6 hr 50 mg/ 6 hr	72 hr 1 mo	Complete defervescence and disappearance of sweats until death
F20415 53/M	5	Generalized adenopathy, hepatomegaly, mediastinal mass, intermittent fever of 98.6-102.2 F (37-39 C)	chlorambucil, mannitol mustard, mechlorethamine HCl, prednisone	sodium oxacillin, kanamycin sulfate, fluoxymesterone, prednisone	None None None None	50 mg/ 8 hr		Complete defervescence
G04841 71/M	1	Generalized superficial adenopathy, hepatosplenomegaly, anemia, intermittent fever of 100.4-102.2 F, marrow infiltration	None	cyclophosphamide prednisone, chloramphenicol, tetracycline, streptomycin sulfate	None None None None None	50 mg/ 8 hr	2 doses	Defervescence for 8 hr prior to death
C36126 34/M	13	Bone pain, splenomegaly, anemia, intermittent fever of 98.6-102.2 F	x-ray, mechlorethamine HCl, melphalan, prednisone, chlorambucil, cyclophosphamide	fluoxymesterone, prednisone, cyclophosphamide, procaine penicillin G, aspirin, isoniazid	None None None None Incomplete None	25 mg/ 6 hr	3 wk	Complete lysis when able to take drug; return of fever when drug omitted
F70791 38/M	4¼	Axillary adenopathy, hepatomegaly, anemia, bone involvement (blastic), intermittent fever of 98.6-102.2 F	chlorambucil, prednisone, vinblastine sulfate, fluoxymesterone	prednisone, vinblastine sulfate	None None	25 mg 2 × daily	4 mo	Only rare temperature elevation
B38447 74/F	2	Superficial adenopathy, hepatomegaly, anemia, intermittent fever of 98.6-102.2 F	chlorambucil, melphalan, prednisone	chlorambucil, prednisone, ampicillin, sodium colistimethate	None None None None	25 mg/ 6 hr	2 mo	Complete lysis of fever and remained afebrile until death
G13056 45/M	1⅓	Retroperitoneal nodes, typical Pel-Ebstein fever, shaking chills	x-ray, mechlorethamine HCl, prednisone, chlorambucil	prednisone, tetracycline, streptomycin sulfate	None None None	25 mg/ 8 hr 50 mg	72 hr 3 wk	Partial control of fever Complete defervescence
F49205 30/M	3	Generalized adenopathy, hepatosplenomegaly, anemia, relapsing (Pel-Ebstein) fever	x-ray, chlorambucil, melphalan, mechlorethamine HCl, prednisone	prednisone, chlorambucil	None None	25 mg 2 × daily 50 mg 4 × daily	7 days 4 wk	Complete defervescence and remained afebrile until death

RESULTS

All nine patients treated with indomethacin had prompt control of fever (Table). Defervescence occurred consistently within 24 hours and some patients became afebrile even more rapidly. Subnormal body temperatures were seen and frequently persisted, but without hypotension or other clinicial manifestations of shock.

The patients often recognized and reported symptomatic improvement as chills and night sweats disappeared. These benefits continued during the period of indomethacin therapy and in some instances could be maintained for as long as several months. When this agent was omitted, fever promptly recurred in 12 to 24 hours, but again responded with reinstitution of therapy. Drug resistance was not observed.

Objective evidence of an effect on the primary disease did not seem to occur in relation to indomethacin therapy. Six patients studied late in the course of their illness died of progressive disease, although fever was controlled.

During these short trials there was no major untoward effect observed. One patient reported lightheadedness and another, mild nausea. In no instance was it necessary to discontinue indomethacin because of inadequate response of untoward drug effect.

REPORT OF CASES

Case 1 (G10253).—A 34-year-old bank employee was hospitalized in April 1961 for evaluation of a febrile illness. The fever subsided spontaneously and a diagnosis was not made. Six months later he developed cervical lymphadenopathy but remained asymptomatic until July 1963, when he developed fever, night sweats, and weight loss. Biopsy of a left cervical node revealed a histological picture compatible with Hodgkin's granuloma. In August 1963, x-irradiation therapy was directed to the left cervical area. The enlarged cervical nodes regressed, but the fever, chills, and night sweats continued. A course of mechlodethamine hydrochloride administered intravenously in October of the same year resulted in brief symptomatic improvement, but fever and chills returned. Prednisone, 60 mg/day, and aspirin, 600 mg/4 hr, did not influence the fever. In early November 1963, the patient was referred to the Duke Medical Center, Durham, N.C.

Physical examination revealed a pale, acutely ill man with signs of recent weight loss. Blood pressure was 112/88 mm Hg; pulse, 116 beats per minute; temperature, 103.2 F (39.6 C); respirations, 20 per minute. There was a well healed scar from a previous node biopsy, but the only enlarged lymph node, measuring 1.0×1.0 cm, was found in the right axilla. The lungs were clear to percussion and auscultation, and the heart was within normal limits. The liver and spleen were not palpably enlarged.

Peripheral blood studies disclosed the following values: hemoglobin 11.6 gm/100 cc; hematocrit 37%; the white blood cell count (WBC) 2,740/cu mm; platelet count 120,000/cu mm, with a WBC differential of 67 polycytes, 19 lymphocytes, and 14 monocytes. Red blood cells (RBCs) showed moderate variation in size and shape and WBCs appeared normal. The sternal marrow was moderately hypocellular with increased plasma cells and lymphocytes. Stainable iron was present. The urine contained protein but with an essentially normal sediment. Blood urea nitrogen (BUN) was 23 mg/100 cc. Liver-function studies were normal except for a slightly elevated serum glutamic oxaloacetic transaminase (SGOT) value of 65 units. Chest film was normal and gastrointestinal series revealed no intrinsic deformity, though the stomach was displaced somewhat by an enlarged spleen. Films of a skeletal x-ray survey and an abdominal lymphangiogram were normal.

During the first few days of hospitalization, the patient continued febrile without evidence of an intercurrent infection. The fever was not influenced by high doses of corticosteriods and aspirin. On the third hospital day the patient was given indomethacin resulting in control of fever for the first time. Whenever a dose was omitted or lost, as in the emesis associated with mechlorethamine hydrochloride therapy, the patient again became febrile (Fig 2). Corticosteroid dosage was tapered and the administration of aspirin discontinued. The fever and chills did not recur with continued indomethacin therapy.

Case 2 (F20415).—In September 1959, a left cervical mass developed in a 53-year-old farmer from Cherryville, NC. After progressive enlargement of the neck mass during seven months, the patient presented to Duke Hospital in April 1960. There were no constitutional symptoms.

Physical examination revealed a 4.5-×4.2-cm left anterior cervical node, bilateral axillary nodes, and a spleen which measured 2.0 cm below the left costal margin during respiratory rest in a line 10.0 cm from the midline.

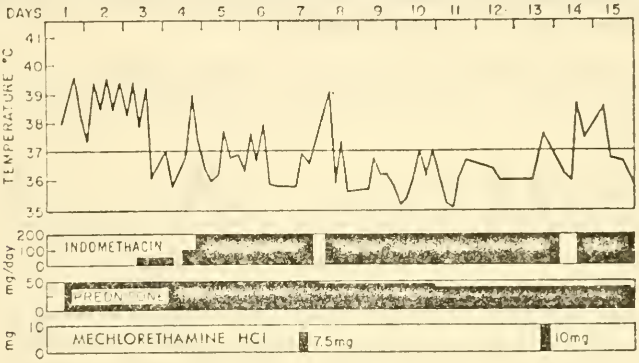


Figure 2.—Temperature response to indomethacin (case 1). Emesis on two occasions following mechlorethamine hydrochloride therapy resulted in loss of indomethacin and return of fever.

Biopsy findings of a lymph node specimen were considered compatible with Hodgkin's granuloma. The patient was initially treated with chlorambucil, 12 mg/day, and a good response (greater than a 50% reduction in measurable parameters of disease) was noted. One year later, the lymph nodes gradually increased in size and a trial with mannitol mustard administered intravenously failed to modify the disease. During the next two years the patient was treated with intermittent courses of mechlorethamine hydrochloride and interval maintenance therapy with chlorambucil. Although brief objective responses were noted and the patient continued to do well subjectively, overall disease progression continued. In July 1964, the patient developed anemia and despite continuous chemotherapy the lymph nodes and the spleen enlarged further. Biopsy of a marrow specimen revealed marked fibrosis with replacement of normal marrow elements. During the next five months alkylating agents, prednisone, and androgen therapy were of limited benefit. In November 1964, the patient was readmitted to the hospital with chills, fever, weakness, and progressive enlargement of the lymph nodes and spleen. During the next month intensive therapy with mechlorethamine hydrochloride resulted in a decrease in size of the lymph nodes and the spleen. The anemia was modified by transfusions. The possibility of intercurrent infection was eliminated during the 30-day period of observation in the hospital, but chills and hectic fever continued unchanged. In early January 1965, indomethacin therapy was started while prednisone and intermittent courses of mechlorethamine hydrochloride were continued. Within 24 hours the temperature returned to normal, and the patient remained afebrile except during intervals when indomethacin was intentionally and temporarily discontinued (Fig. 3).

COMMENT

The results of this study indicate that indomethacin is a potent antipyretic in the nine cases of Hodgkin's disease studied. The mechanism of the antipyretic action is presently unexplained. It evidently was not associated with regression of disease activity. The clinical safety of the drug is an apparent advantage over previously used compounds such as aminopyrine and phenylbutazone.

A complete dose response curve was not obtained. However, it is apparent from these studies that the drug must be given in divided doses during the day. Eight hours appears to be the maximal interval, but optimal control of fever is achieved when the drug is administered every six hours. An effective regimen is 25 to 50 mg given at six-hour intervals.

At this recommended dose schedule serious untoward reactions were not observed. Gastrointestinal disturbances and headaches cited in other studies[13, 20] were not encountered in this group of patients.

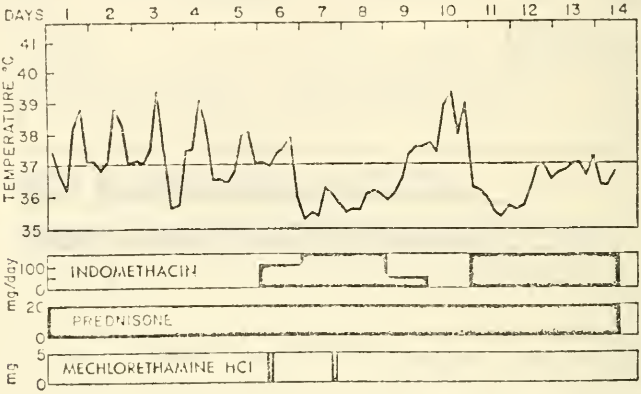


FIGURE 3.—Temperature response to indomethacin (case 2). Fever initially controlled by indomethacin relapsed rapidly with cessation of therapy. Reinstitution of therapy again resulted in prompt control of fever.

One patient with Hodgkin's disease and severe pruritus was given indomethacin for this symptom and failed to improve. Further trial of the drug for this complaint might be necessary.

Since fever can be used as a guide to the effectiveness of chemotherapy with cytotoxic agents, symptomatic treatment perhaps should be withheld initially. Only after a complete evaluation of the disease, exclusion of complicating infections, and an adequate trial of appropriate chemotherapy should a nonspecific antipyretic be used. Defervescence does not exclude the possibility of an underlying infection.

(The indomethacin used in this investigation was supplied as Indocin through Nelson H. Reavey Cantwell, MD, from the Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pa.

Generic and Trade Names of Drugs

Aminopyrine—*Pyramidon.*
Phenylbutazone—*Butazolidin.*
Melphalan—*Alkeran.*
Prednisone—*Deltasone, Deltra, Meticorten, Paracort.*
Mechlorethamine hydrochloride—*Mustargen Hydrochloride.*
Vincristine sulfate—*Oncovin.*
Chlorambucil—*Leukeran.*
Fluoxymesterone—*Halotestin, Ora-Testryl, Ultandren.*
Tetracycline—*Achromycin, Panmycin, Polycycline, Steclin, Tetracyn.*
Kanamycin sulfate—*Kantrex.*
Methylprednisolone—*Medrol.*
Sodium Oxacillin—*Prostaphlin, Resistopen.*
Cyclophosphamide—*Cytoxan.*
Chloramphenicol—*Chloromycetin.*

Procaine penicillin G—*Depo-Penicillin, Lentopin, Wycillin.*
Isoniazid—*Hyzyd INH, Isoniazid, Niconyl, Nicozide, Nydrazid, Rimifon, Tyrid.*
Vinblastine sulfate—*Velban.*
Ampicillin—*Penbritin, Polycillin.*
Sodium colistimethate—*Coly-Mycin Injectable.*

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[Correspondence]

[From British Medical Journal, Jan. 1, 1966]

LEUCOPENIA AND INDOMETHACIN

SIR.—I wish to report the occurrence of a febrile illness, with late leucopenia in a patient on indomethacin therapy in general practice.

A 52-year-old housewife with a 27-month history of rheumatoid arthritis developed an acute pyrexia of 102° F. (38.2° C.) without initial localizing signs. She had received indomethacin for the previous eight months in a daily dosage of 50 mg. for the first five months, 75 mg. for three months, and 100 mg. for two weeks prior to the febrile illness. Prior to the indomethacin she had received hydroxychloroquine sulphate and phenylbutazone for 12 and seven months, respectively. There was no known contact with any febrile illness nor did any of the patient's contacts develop a similar illness.

On the third day the temperature rose to 103° F. (39.5° C.) and she complained of a very painful throat, the only objective finding being a slight diffuse infection of the pharynx. Indomethacin was stopped and phenoxymethylpenicillin given in a dosage of 250 mg. four times daily. The fever and sore throat settled gradually and she remained afebrile after the seventh day, though prostrated. There were no chest symptoms or signs at any time. A blood count on the ninth day showed Hb 81%, white blood cells 2,700/c.mm. (neutrophils 24%, lymphocytes 67%, monocytes 9%; no primitive white blood cells seen; red cells showed slight anisocytosis). On the eleventh day white blood cells were 2,800/c.mm. (neutrophils 40%, lymphocytes 60%). On the seventeenth day she was quite well when the Hb was 80%, white blood cells 6,500/c.mm., with a normal differential.

In the absence of serological tests the cause of this patient's illness remains speculative, but it seems worth inquiring if others have noted a similar association, which has not to my knowledge been previously reported—I am, etc.,

BIRMINGHAM 22.

D. MILLINGTON.

[From British Medical Journal, Jan. 8, 1966]

FURTHER EXPERIENCE WITH INDOMETHACIN IN THE TREATMENT OF RHEUMATIC DISORDERS

(By M. Thompson,* M.D., M.R.C.P.; J. S. Percy,*† M.B., B.S., M.R.C.P. Ed.)

Indomethacin (Indocid) is an indole-3-acetic acid derivative, which was found to have powerful anti-inflammatory and analgesic properties, and which has been under clinical investigation since October 1962. Several controlled trials demonstrated that it had some value in the treatment of rheumatic disorders, being significantly more effective than placebos in the treatment of both rheumatoid arthritis (Wanka, Jones, Wood, and Dixon, 1964) and osteoarthrosis of the hip (Wanka and Dixon, 1964). When indomethacin was compared with phenylbutazone in a controlled trial in rheumatoid arthritis (Percy, Stephenson, and Thompson, 1964) no significant difference was noted either in terms of relief of pain or by improvement in grip-strength, but side-effects were commoner with indomethacin. All these early studies were undertaken with indomethacin in tablet form, and it was found that this preparation had disadvantages owing to variable dissolution rates of the tablets and erratic absorption from the gastro-intestinal tract. The use of capsules, available since September 1963, overcame these difficulties, and subsequent clinical experience indicated that a commensurate clinical effect could be obtained with a lower dosage of indomethacin in capsule form than when it was administered as tablets (Thompson, 1964).

Experience with other drugs used in the treatment of chronic rheumatic disorders, notably with the predni-steroids, has shown that potency of a drug does not establish its place as the therapeutic agent of choice. Controlled clinical trials of short duration serve to estimate the immediate value of a drug and any early side-effects, but it is only by means of long-continued clinical experience that answers may be provided to such questions as the frequency, severity, and nature of adverse side-effects, optimum dosage levels, and the indications for or against the use of the drug. As indomethacin became available for use in general practice in March 1965 we are recording our experience of a group of 137 patients treated with 25-mg. capsules during the 82 weeks from September 1963 to April 1965.

The diagnoses of the 137 patients are listed in Table I, the majority being rheumatoid arthritis or osteoarthrosis. All patients were treated in the out-patient department and were seen at intervals of one to eight weeks according to the severity of their symptoms, the duration of their treatment, and the presence of side-effects. Regular urine analysis, blood counts, and liver-function tests were done in all patients receiving treatment for one month or longer. Indomethacin was administered in 25-mg. capsules taken after meals with an adequate amount of fluid. Previous experience had shown that a progressive dosage regime reduced the incidence of early side-effects, so treatment was inaugurated with one capsule daily after breakfast for three to seven days, increasing thereafter to two capsules taken at 12-hourly intervals, and later to three or more capsules daily, in divided dosage. When indomethacin was given to patients currently receiving phenylbutazone, the latter preparation was discontinued. Patients on aspirin or predni-steroids maintained dosage of these preparations at the same level initially, then reduced or stopped them if the response to indomethacin was satisfactory. The results of our experience are summarized under the headings of rheumatoid arthritis, osteoarthrosis, miscellaneous rheumatic disorders, and side-effects.

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TABLE I.—*Composition of the Group of 137 Patients*

Rheumatoid arthritis	70	Psoriatic arthritis	2
Osteoarthrosis	50	Polymyalgia rheumatica	2
Ankylosing spondylitis	4	Systemic sclerosis	1
Gout	3	Shoulder-hand syndrome	1
Cervical spondylosis	3	Reiter's syndrome	1

RHEUMATOID ARTHRITIS

Seventy patients suffering from classical or definite rheumatoid arthritis, according to the American Rheumatism Association (1959) criteria, received indomethacin for periods ranging from 1 to 82 weeks, the mean duration being 33 weeks. The average daily maintenance dosage was 75 mg., with a range from 25 to 150 mg. The results of treatment are shown in Table II. Three patients developed intercurrent illnesses unrelated to the rheumatoid condition or to therapy, but indomethacin was withdrawn to avoid the complicating factor of a new drug in their management, so these patients were not included in the assessment of outcome. Of the remaining 67 patients 27 (40%) continued the treatment, and to this number should be added the three patients who obtained a complete remission, giving a total of 30 (44%) for whom treatment may be classed as completely or reasonably successful.

TABLE II.—COMPARISON OF RESULTS OF TREATMENT IN RHEUMATOID ARTHRITIS AND OSTEOARTHROSIS

Outcome	Rheumatoid arthritis patients		Osteoarthrosis patients	
	Number	Percent	Number	Percent
Continued therapy	27	[1]40	31	[1]63
Stopped; full remission	3	[1]4	3	[1]6
Stopped; side effects	22	33	11	23
Stopped; lack of benefit	15	22	4	8
Total	67		49	
Patients estimate of benefit:				
Satisfactory	18	[1]26	28	[1]55
Fairly good	28	40	14	29
Slight or absent	24	34	8	16
Total	70		50	

[1] Indicates significant differences between the 2 columns.

Note: 3 rheumatoid patients who stopped treatment owing to intercurrent illness and 1 osteoarthrotic patient lost to follow up were not included in the assessment of outcome.

The patient's estimate of benefit was based upon several factors, notably relief of pain, reduction of morning stiffness, and comparison with previous therapy when this had been replaced by indomethacin. The influence of side-effects was excluded from this assessment. *By these criteria 18 (26%) felt that indomethacin was the most effective drug they had received, 28 (40%) considered it to be reasonably effective, and 24 (34%) found it to be relatively or absolutely ineffective.*

Side-effects occurred in 26 (37%) patients (Table III), and necessitated withdrawal of treatment in 22. Inadequate clinical effect was the reason for stopping treatment in a further 15 (22%), making a total of 37 (55%) who stopped taking the drug because it was unsatisfactory. These two factors of side-effects and poor clinical response are to some extent interdependent, as lack of benefit led in eight cases to increasing the dosage to a point where satisfactory analgesic effect was obtained only by the development of unacceptable side-effects.

OSTEOARTHROSIS

Fifty patients suffering from osteoarthrosis were treated for periods ranging from 2 to 82 weeks, the mean duration being 28 weeks. The average daily maintenance dosage was 75 mg., the range being 25 to 125 mg. The results of treatment are shown in Table II. Only one patient was lost to follow-up through failure to attend. Of the remaining 49 patients 31 continued with treatment, and to these may be added the three patients who obtained a complete remission of symptoms, making a total of 34 (69%) in whom the outcome was regarded as completely or reasonably successful.

The patients' estimate of benefit was based upon the factors of pain relief, reduction of stiffness, improvement in functional capacity, and comparison with previous therapy. By these criteria 28 (56%) patients thought that indomethacin was satisfactory, 14 (28%) found it to be fairly good, and only 8 (16%) considered it to be relatively or absolutely ineffective.

Side-effects occurred in 14 (28%) patients and were responsible for the withdrawal of the drug in 11. The incidence of side-effects was lower than in the rheumatoid group, but not significantly so. The number of patients withdrawn because of inadequate effect was much lower in the osteoarthritic patients (8%) than in those suffering from rheumatoid disease (22%), and this difference was statistically significant ($\chi^2=4$, $P<0.05$). When the outcome of therapy was compared there was a significantly favourable result for the osteoarthritic group in comparison with the rheumatoid patients ($\chi^2=6$, $P<0.02$). Furthermore, when the patient's estimate of benefit was considered, the numbers claiming satisfactory benefit were significantly higher in the osteoarthritic group ($\chi^2=10$, $P<0.005$).

MISCELLANEOUS GROUP

The composition of this group of 17 patients is shown in Table I, and these patients received treatment for periods ranging from 1 to 55 weeks, the mean being 13 weeks. The average dosage was 87 mg. daily, the range being 50 to 150 mg. Seven patients experienced side-effects compelling withdrawal of the drug in six cases, and in a further two it was withdrawn because of inadequate benefit. Two patients stopped taking indomethacin when they left the district, and in three the drug was stopped because of satisfactory remission of symptoms. Four patients continued to take indomethacin. The numbers involved are too small to permit detailed analysis of the results in the group as a whole or in the various diagnostic subgroups, but some observations on the outcome are presented.

Of the two patients suffering from psoriatic arthritis, one improved and continued with treatment but the other developed side-effects within two weeks and had to stop. A similar response was observed with the two patients suffering from polymyalgia rheumatica, one of whom developed side-effects, while the other found indomethacin to be effective and was able to stop steroid therapy. None of the three patients with cervical spondylosis obtained striking benefit, but all had complicating illnesses and had been refactory to previous drugs and physiotherapy.

Four patients suffering from ankylosing spondylitis were treated and three had to discontinue because of side-effects, the therapeutic response being rated as satisfactory, good, and slight respectively. The fourth patient continued treatment with satisfactory effect.

A strikingly favourable response was obtained in the three patients treated for gout: acute symptoms were rapidly brought under control in the two who received daily maintenance doses of 75 and 125 mg. respectively, and were then able to stop treatment in complete remission; the third patient with chronic gout was experiencing intermittent painful episodes, and these have remained suppressed while treatment has continued with a maintenance dosage of 50 mg. daily.

The patient suffering from shoulder-hand syndrome following coronary thrombosis obtained fairly good relief of symptoms with a maintenance dosage of 100 mg. daily given for seven weeks, and the patient with Reiter's syndrome continued therapy with good effect on a dosage of 75 mg. daily. The last patient in this group, who had a painful arthropathy complicating systemic sclerosis, developed side-effects on minimal dosage of indomethacin.

SIDE EFFECTS

The number and the nature of the side-effects encountered among 137 patients are listed in Table III. A total of 70 symptoms were recorded in 47 (34%) patients, and compelled withdrawal of therapy in 39 (28%) cases. Though the incidence was lower in the osteoarthritic group, there were no significant differences between the three groups in either the incidence or character of the symptoms. There were no deaths from any cause in any patient receiving indomethacin during the entire period of the trial. Furthermore, no significant or sustained adverse effects were noted on the haematopoietic, hepatic, or renal organs as judged by repeated laboratory investigations.

TABLE III.—SIDE EFFECTS ATTRIBUTED TO INDOMETHACIN

	Rheumatoid Arthritis	Osteoarthrosis	Miscellaneous	Total
Number of patients	70	50	17	137
Number of side effects	26	14	7	47
Percent of side effects	37	28	41	34
Headache	14	4	1	19
Vertigo or lightheaded	13	4	3	20
Epilepsy	1			1
Coma		1		1
Depression	2	2		4
Hallucinations		1		1
Nausea	7	3	4	14
Vomiting	2		1	3
Dyspepsia		1		1
Diarrhea	1			1
Melaena	1			1
Perforation		1		1
Rash	1	2		3
Total	42	19	9	70

The side-effects could be classified in three main groups, which, in order of frequency, were neurological, gastro-intestinal, and dermatological. The commonest symptom was headache, which was variable in its severity, character, and distribution and was not associated with any apparent vascular changes. Most frequently the headache was located centrally in the skull or at the vertex and occurred on first waking or shortly after the first capsule of the day had been taken. In the majority of cases the headache was associated with vertigo, lightheadedness, or a feeling of slight confusion. In the most severe cases there was associated nausea, malaise, and vomiting, variously described as motion-sickness or moderate inebriation. When the headache was slight it was possible to avoid it by temporary reduction of the dosage, and five patients were able to continue treatment after this had been done. Seven patients experienced major neurological disturbances, four becoming severely depressed and three developing coma, epilepsy, and hallucinations respectively. The four women who developed depressive symptoms did so after long periods on treatment, the average being 37 weeks before symptoms developed. In the other three cases the maintenance dosage had been 100 mg. daily or above.

Depressive symptoms developed insidiously in all four patients who, lacking insight into the cause of their trouble, continued to take the capsules. One patient stated that she had contemplated suicide. The depression cleared rapidly when the capsules were stopped. Two of these patients later resumed indomethacin therapy in lower dosage, without any recurrence of depression during eight weeks' therapy. This was justified on the grounds that indomethacin had given the most benefit in the treatment of their arthritic symptoms and that both these patients and their relatives were alerted to the necessity for drug withdrawal should any neuro-psychiatric symptoms recur. The patient who became comatose was a 43-year-old man who had taken indomethacin for two weeks, had reached the 75 mg. daily dosage level, and was not taking any other drugs. He became comatose within half an hour of feeling confused, and three hours after taking the first capsule of that day, and may have taken an extra capsule. The coma began to clear in three hours and he remained stuporous until the following day. He was admitted to hospital, where no localizing signs were found, and investigations failed to reveal any cause, other than indomethacin, for his condition.

One patient, a man aged 52, had three epileptiform seizures while taking indomethacin. The first was a Jacksonian attack involving the right arm, and this occurred during the second week of therapy. The second attack began with a Jacksonian fit but in addition involved some transient paresis of both legs. The third seizure occurred during the third week of treatment, when the dosage was 75 mg. daily, and started as a Jacksonian attack but progressed to a grand-mal fit with brief loss of consciousness. Subsequent neurological investigation and electroencephalographic examinations were negative and the patient has had no further seizures since stopping indomethacin one year ago.

The patient who experienced visual and auditory hallucinations was a 72-year-old woman who had been taking 50 mg. of indomethacin daily for 31 weeks with good effect for an osteoarthrotic hip. She saw and conversed with various friendly ghosts whose visitations were becoming more frequent until the capsules were stopped. This patient also had atherosclerosis and was receiving methyldopa in the treatment of hypertension, but she has not had further hallucinations in the three-month period since indomethacin was stopped.

As most of the 14 patients complaining of nausea and two of the three cases of vomiting were associated with headache and vertigo, the incidence of side-effects originating in the gastro-intestinal tract was small. The only major incident was perforation of an acute duodenal ulcer in a 67-year-old woman who had taken 75 mg. of indomethacin daily for 14 weeks, and had no preceding history of dyspepsia. This patient later continued therapy with indomethacin by suppositories, 100 mg. daily, with relief of her hip pain.

One patient, who had a long previous history of peptic ulceration and had been unable to take other analgesics and anti-inflammatory drugs, took indomethacin tablets for 14 weeks and then capsules for 26 weeks before she had a slight melaena. As indomethacin gave such symptomatic relief she later tried suppositories but was unable to retain these.

Three patients developed a diffuse erythematous mascular rash, associated with mild stomatitis in one case. In all cases the rash cleared within a day of discontinuing treatment. One of these patients resumed taking indomethacin on her own initiative but stopped it when the rash occurred within a few days. Possible, but not proved, side-effects included (*a*) the occurrence of furunculosis in two men, which cleared while they continued with indomethacin; (*b*) the aggravation of leg oedema in two women, both of whom were receiving steroid therapy, and (*c*) the aggravation of pre-existing mild diabetes in a man.

DISCUSSION

It is clear from reported clinical experience that indomethacin is a powerful compound, capable of giving relief of symptoms and reduction of inflammatory signs in several rheumatic disorders. The most striking reduction of inflammatory signs has been noted in gout and in acute articular exacerbations of rheumatoid disease. However, the greatest benefit has been obtained in osteoarthrosis, particularly when the hip-joints were involved. The results of treatment were significantly better in the osteoarthrotic than in the rheumatoid group when judged by the criteria of (*a*) fewer failures owing to lack of effect, (*b*) numbers of patients able to continue with satisfactory relief of symptoms without experiencing side-effects, and (*c*) the patients' own estimates of benefit.

Of the total group of 137 patients 39 (28%) had to stop treatment because of unacceptable side-effects and 21 (15%) because of lack of benefit, while six patients stopped treatment for other reasons. Nine patients stopped because of satisfactory remission and 62 continued to take the drug, making 71 (52%) in whom the outcome has been satisfactory. This proportion of success must be judged against the background of the previous history of these patients, as no patient was treated with indomethacin *ab initio* but only when they presented a therapeutic problem. Thus all 70 rheumatoid patients had received aspirin, 35 had been given oral predni-steroid therapy, and 44 had been treated with one or more anti-inflammatory preparations—for example, phenylbutazone, gold salts, or chloroquine preparations. In the miscellaneous group of 17 patients 14 had received aspirin, 5 oral predni-steroids, and all 17 had taken other anti-inflammatory preparations, mainly phenylbutazone. In the group of 50 patients suffering from osteoarthrosis the previous therapy had comprised aspirin in 48 cases, oral predni-steroid therapy in 5, and other anti-inflammatory drugs in 40. In these circumstances the results obtained indicate that indomethacin has provided a most useful additional therapy in the management of osteoarthrosis, gout, and some patients suffering from rheumatoid arthritis. Although in our experience gout treated by capsules of indomethacin has been limited to three cases, the results obtained in these patients, supplemented by our experience with three patients treated by tablets, fully confirm the beneficial effects recorded by Hart and Boardman (1963), who noted the particular value of indomethacin in controlling acute gouty symptoms.

In general, the response to indomethacin could be predicted within the first few days of treatment, as those who were going to obtain substantial benefit often responded to small doses. Daily maintenance dosage of 50 or 75 mg. was usually adequate, occasional patients requiring 100 mg. or more. The absolute maximum dosage that was used was 150 mg. daily. The limiting factor was the development of undesirable effects, which became more frequent as dosage increased. The value of a slowly progressive dosage regime has already been demonstrated in the use of tablets in reducing the incidence of headache in the early stages of treatment (Percy *et al.*, 1964). A further advantage of the initial low-dosage regime is that patients extremely intolerant of indomethacin will be detected early, so that though unacceptable side-effects occur the risk of major trouble is limited. Five patients in our series had troublesome side-effects of headache and vertigo while on the minimum dosage of 25 mg. daily and were compelled to stop treatment. This is a point of considerable importance, as the headache, vertigo, and "muzziness" so commonly encountered during indomethacin therapy may occur acutely and episodically, and patients should be warned of the dangers of traffic, either as pedestrians or drivers.

We found the clinical response to indomethacin to be similar in many respects to that seen with phenylbutazone, which has been used extensively in the treatment of generalized osteoarthrosis, osteoarthrosis of the hip, acute gout, rheumatoid arthritis, particularly with actively inflamed large joints, and ankylosing spondylitis. The fact that indomethacin is a rapidly effective, non-steroidal, anti-inflammatory agent, like phenylbutazone, makes it a useful alternative to prednisteroid therapy.

As with many other drugs used in the treatment of chronic rheumatic disorders, indomethacin causes undesired effects which are particularly apt to occur in the early stages of treatment. Fortunately most of these are trivial and clear rapidly after withdrawal of the drug. In view of the occurrance of severe neurological disturbance in seven of our cases we feel that it would be unwise to ignore and dangerous to suppress the headache and associated symptoms so commonly encountered. If these cannot be avoided by gradual induction or by subsequent reduction of dosage, they must be taken as an indication for stopping the drug. It would seem reasonable to insist that indomethacin should only be given with caution to any patient with a history of depressive illness. Active or recent peptic ulceration should be regarded as an absolute contraindication, and therapy should not be resumed in any patient who exhibits a rash during treatment.

SUMMARY

Clinical experience with indomethacin during a period of 18 months in a series of 137 patients comprising 70 with rheumatoid arthritis, 50 with osteoarthrosis, and 17 with miscellaneous rheumatic disorders is recorded. A progressive dosage regime was used beginning with 25 mg. daily, and the average daily maintenance dosage was 75 mg.

Striking benefit was obtained in osteoarthrosis with a satisfactory outcome of treatment in 69% of cases, which was significantly better than the rheumatoid group where 44% were satisfactory. An excellent response was also seen in three patients suffering from acute gout.

A total of 70 side-effects occurred in 47 patients and compelled withdrawal of treatment in 39 (28% of the total group). The principal undesired symptoms were headache associated with vertigo, etc., but major neurological disturbance occurred in seven cases. All these symptoms subsided rapidly on withdrawal of therapy. There was one instance of slight melaena, one perforated ulcer, and three rashes developed during therapy.

Indomethacin is thought to be a useful addition to the range of drugs used in the management of certain rheumatic disorders, notably in osteoarthrosis, acute gout, rheumatoid arthritis, and spondylitis.

We wish to thank Dr. R. Hodgkinson, of Merck Sharp & Dohme, Hoddeson, Herts, for his co-operation and for supplies of indomethacin capsules. We also thank Drs. M. Hall, R. A. H. Morison, and R. A. Sutton for help in the care of the patients, and Miss P. Port for secretarial assistance.

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[From Clin-Alert, Jan. 20, 1966]

INDOMETHACIN—PREDNISOLONE

[No. 16]

"An arthritic patient with a history of duodenal ulcer, present 20 years earlier, developed dyspepsia after receiving indomethacin, 200 mg. and predinisolone, 8 mg. daily for about six months. This was followed by hematemesis which required blood transfusions. In several cases of hematemesis previously reported, this combination of drugs was used."—Hart & Boardman (London, Eng.), British M.J. 2:1281 (Nov. 27), 1965.

[From Clin-Alert, Feb. 26, 1966]

INDOMETHACIN

[No. 52]

A. *Leukopenia:* "A 52-year-old woman with rheumatoid arthritis received indomethacin (Indocin) in daily dosage of 50 mg. for five months, 75 mg. for three months, and 100 mg. for two weeks prior to developing a febbrile illness associated with a very sore throat. Indomethacin was withdrawn and antibacterial therapy instituted. On the ninth day of the acute illness the white cell count was 2,700/cu. mm. (neutrophils 24%; lymphocytes 67%; monocytes 9%; no primitive white cells). By the seventeenth day the white cell count had risen to 6,500/cu. mm. with a normal differential count. Although the nature of the patient's illness remains obscure, '. . . it seems worth inquiring if others have noted a similar association, which has not to my knowledge been previously reported.' "—Millington (Birmingham, Eng.), British M.J. 1:49 (Jan. 1), 1966.

B. *Neurological Effects:* "Of 137 rheumatic patients treated with indomethacin, 39 (28%) experienced undesirable side effects of sufficient severity to warrant discontinuing the drug. The most frequent untoward effects were headache associated with vertigo, etc. Major neurological disturbances occurred in seven cases (severe depression in four patients and coma, seizures, and hallucinations in each of three patients). Symptoms subsided promptly upon withdrawal of the drug. The authors state that it is unwise to ignore and dangerous to suppress the headache and associated symptoms so commonly encountered in patients receiving indomethacin. If such symptoms can not be avoided by gradual induction or by subsequent reduction in dosage, they must be considered an indication for stopping the drug. In addition, indomethacin should be employed cautiously in patients with a history of depressive illness. Active or recent peptic ulceration is an absolute contraindication to use of indomethacin. Further, treatment with the drug should not be resumed in patients who develop a drug rash during treatment (as did three patients in this study). It should be noted that no significant or sustained adverse effects were noted on the hematopoietic, hepatic, or renal system of patients observed by these authors."—Thompson & Percy (Newcastle upon Tyne, Eng.), British M.J. 1:80 (Jan. 8), 1966.

[Medical Memoranda]

[From British Medical Journal, Apr. 16, 1966]

ACTIVATION OF LATENT INFECTION BY INDOMETHACIN: A REPORT OF THREE CASES

Indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methlindol-3-acetic acid, is a potent, non-steroid, anti-inflammatory agent which has given encouraging results in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteorathritis, and gout (Hart and Boardman, 1963). Since its introduction in 1963 it has been used with increasing frequency and is now prescribed in this hospital more often than any other antirheumatic drug except aspirin.

Toxic side-effects are common with indomethacin. In the early trials the use of the compressed tablet and excessively high doses (200–300 mg. daily) often resulted in serious complications such as gastro-intestinal haemorrhages and perforated peptic ulcer (Norcross, 1963; Lövgren and Allander, 1964; Wanka *et al.*

1964). With the use of the drug in powder form in gelatin capsules and doses of 75–100 mg. daily serious side-effects have been reduced, though by no means eliminated, and the milder complaints such as headache, faintness, drowsiness and giddiness, and nausea and dyspepsia, though still relatively common, are usually not serious enough to necessitate withdrawal of the drug.

In spite of the known tendency for the more potent anti-inflammatory compounds to cause a flare-up of existing but controlled infection, there has so far been no report of this complication occuring with indomethacin. Three such cases have now been encountered in this unit and are described below.

CASE 1

A shopkeeper aged 39 was admitted to hospital for a right inguinal herniorrhaphy. Soon after the operation he developed pain in the right hip which became progressively worse over the next two months.

Examination then revealed a 35° flexion deformity of the right hip with movements markedly restricted in every direction. The herniorraphy scar had healed and general examination showed no other abnormality. He was aprexial and his pulse rate was normal.

Radiographic examination of the hip showed a slight blurring of the outlines of the femoral and acetabular articular surfaces but no active bone destruction or erosion. The appearances were compatible with either a low-grade infection of the joint or rheumatoid arthritis.

The sedimentation rate (Wintrobe) was 5 mm./hr. The blood picture was normal. Blood cultures and tests for typhoid and brucellosis were negative. The Mantoux test was negative. Plasma uric acid was 6.8 mg./100 ml. The sheep cell agglutination test was negative but the latx fixation test was positive; C-reaction protein was 2-plus positive. On being repeated, the latex fixation test was negative.

Two weeks after admission, when the patient's condition was unchanged and he was still being investigated, he was inadvertently included in a group of patients to be treated with indomethacin. After receiving 100 mg. daily for six days he suddenly became very ill, his temperature rose to 100° F. (37.8° C.), and the hip became excruciatingly painful, with passive movements now quite impossible. A further radiograph showed deterioration of the joint with bone destruction along the articular margin of the femur.

Open drainage of the hip and synovial biopsy were carried out forthwith. Thin pus and flakes of caseous material were encountered in the joint.

Histological examination of the synovium showed a granulomatous reaction consistent with tuberculosis, and occasional acid-fast bacilli. Mycobacteria were later cultured from the pus.

CASE 2

A manufacturer aged 28 sustained a fracture-dislocation of the right hip in a motor accident in May 1960. The hip was reduced by one operation and a large displaced acetabular fragment was fixed back in position with two screws. After six weeks in a plaster-of-Paris spica he was discharged.

During the next four years he had almost constant mild pain in the hip, with occasional more severe episodes, one of which (in 1962) was associated with a pyrexial illness lasting four days.

In April 1965, 10 days before admission to this unit, he was put on to indomethacin, 100 mg. daily, for the pain in his hip. There was dramatic symptomatic improvement within the first three days. On the eighth day of this treatment, however, he suddenly became severely ill and the pain in his hip recurred with greater severity than ever before.

On admission to hospital his condition was alarming. He was mentally confused, with a temperature of 103° F. (39.4° C.) and a pulse rate of 136. He was dyspnoeic and had all the signs of a bilateral pneumonia. The right hip was held rigid and even the slightest movement caused intense pain.

Radiographic examination of the lungs showed widespread areas of consolidation. Radiographs of the hip showed some blurring of joint outline but no bone destruction.

The haemoglobin estimation was 14.5 g./100 ml., the white cell count 16,000 per c.mm., and sedimentation was 20 mm. (Wintrobe). Blood culture produced a growth of coagulase positive *Staphylococcus aureus*. Vigorous antibiotic treatment resulted in a gradual return to his previous state.

CASE 3

A 63-year-old housewife with long-standing rheumatoid arthritis began to complain of increasing joint pains. Five years before this a similar exacerbation in activity of the disease had been treated by steroids—with disastrous effect, for soon after commencing this treatment she developed a septic arthritis of the right hip-joint. After open drainage of the pus and prolonged antibiotic therapy the infection subsided in the hip, only to recur in the left shoulder. A further course of antibiotics and drainage of pus were required, after which her condition slowly returned to its previous state.

Thereafter any sign of recurring activity of the rheumatoid arthritis was treated with considerable circumspection, and steroids were not used again. At the start of the present attack, however, she was put on to indomethacin, 100 mg. daily. Ten days later she developed severe dyspepsia, and three days after that she complained of intense pain and swelling of the left elbow. On examination she was found to have a septic arthritis of the left elbow-joint. The indomethacin was stopped, she was given erythromycin in large doses, and the arm was splinted to control pain. After three weeks it settled down again and soon afterwards the antibiotic was discontinued. Her symptoms have not recurred for over three months.

COMMENT

The anti-inflammatory action of indomethacin, as evidenced by the inhibition of cotton-pellet granuloma formation in the rat, is considerably stronger than that of either phenylbutazone or hydrocortisone (Winter *et al.*, 1963). Yet, in contrast to hydrocortisone, indomethacin has been shown not to diminish the resistance to infection in the experimental animal, even when given in amounts 100 to 300 times the threshold dose for effective anti-inflammatory activity (Merck Sharp and Dohme, 1964). When, therefore, one considers that the reported incidence of intercurrent infection in humans treated with steroids is far lower than might be expected from the experimental findings (Benedek and Montgomery, 1954; Bennett *et al.*, 1964), it is tempting to discount the possibility of this complication altogether in the case of indomethacin.

The three cases described here invite a reassessment of this precept. In Case 1 a covert infection was brought to light and in Cases 2 and 3 a known or suspected previous infection was reactivated after the administration of indomethacin. Whereas hydrocortisone causes a reduction in antibody formation and phagocytic activity, indomethacin does not produce either of these effects (Marck Sharp and Dohme, 1964). It is presumed, therefore, that the complication encountered in these three cases was due to a breakdown of the local barriers to the spread of infection. This is cause for disquiet and points to the need for further investigation of the effects of indomethacin and greater care in the selection of patients for treatment with a potent drug which is being prescribed with the current abandon.

I would like to thank Mr. S. Sacks and Mr. H. Klein for allowing me to publish the details of Cases 2 and 3 respectively.

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[Council on Drugs]

[From Journal of the American Medical Association, May 16, 1966, vol. 196, No. 7]

A NONSTEROIDAL ANTI-INFLAMMATORY AGENT—INDOMETHACIN (INDOCIN)*

(This statement is an initial assessment of a new drug evaluated on the basis of available evidence. It does not necessarily represent the final opinion of the Council on Drugs, nor does it imply approval, endorsement, or acceptance of the drug.)

Indomethacin is a nonsteroidal agent that is useful for the treatment of certain inflammatory joint diseases. Its use is not necessary when salicylate therapy is effective. When indomethacin is given concomitantly with corticosteroids, the dosage of the steroids often can be reduced. Further controlled trials are needed to determine the usefulness of indomethacin as compared to other anti-inflammatory drugs. Although the adverse reactions associated with this drug are not hazardous, those affecting the central nervous system and gastrointestinal tract may be sufficiently severe to limit its use.

Indomethacin is a new type of nonsteroidal chemical compound that has anti-inflammatory, antipyretic, and analgestic properties.

Present clinical experience indicates that this drug is as effective as the salicylates in patients with rheumatoid arthritis. However, its use is not necessary when salicylate therapy is effective. Although aspirin is still considered the drug of first choice, indomethacin may be tried if aspirin ceases to be beneficial or is no longer tolerated. Doses of aspirin may be taken between regular doses of indomethacin if necessary.

When given alone, indomethacin is more effective in active rheumatoid arthritis than in the inactive "burnt-out" type. In about two thirds of the patients, pain, tenderness, and stiffness decrease and ambulation increases in two to three days. However, some clinicians have found that maximal benefits are not obtained until indomethacin has been given for a month or more. With prolonged administration, 10% to 15% of the patients who responded initially must stop taking indomethacin because of its untoward effects.

It has been reported that indomethacin reduces joint swelling and edema in some patients with rheumatoid arthritis. However, results have been equivocal in the few studies in which objective measurements of joint size were made. The erythrocyte sedimentation rate was not affected.

When given alone, indomethacin is less effective than the corticosteroids in the treatment of rheumatoid arthritis. When given concomitantly, however, the dose of the steroids often can be halved and in some patients completely withdrawn. Thus, indomethacin may be especially useful in patients who have been receiving long-term therapy with corticosteroids. However, the hazards of combined therapy with steroids and indomethacin have yet to be fully evaluated.

Indomethacin has been particularly useful in the treatment of mild to moderate osteoarthritis of the hip joint, a condition that is resistant to all other anti-inflammatory agents. It also appears to relieve the pain of ankylosing spondylitis as effectively as does phenylbutazone (Butazolidin).

Indomethacin produces anti-inflammatory effects in patients with gout and may be as effective as phenylbutazone in its promptness of action and the degree of relief it provides. Because it has produced relief in acute attacks within 48 hours, and because it lacks the untoward effects of colchicine, some clinicians consider it to be the drug of choice for these attacks; however, controlled trials are needed to determine how its effectiveness compares with that of colchicine. Indomethacin may be useful as a supplement to colchicine in the management of severe cases of gout. Whether it is useful as a propylactic agent in gouty arthritis remains to be established.

ADVERSE REACTIONS

Central-nervous-system effects (headaches, usually severe in the morning; vertigo; light-headedness; mental confusion) occur during the early weeks of therapy in about 20% to 30% of patients taking indomethacin. These symptoms may occur within the first few hours after administration or may be delayed for two or three days; they frequently disappear with continued used and are reversible when the drug is discontinued. Generally, these effects are dose-related and are less likely to appear if the daily dosage is 100 mg or less given in divided amounts.

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*Scientific data on indomethacin were supplied to the Council by Merck Sharp & Dohme, West Point, Pa.

Address reprint requests to Secretary, Council on Drugs, American Medical Association, 535 North Dearborn St., Chicago 60610.

Gastrointestinal reactions (nausea, indigestion, epigastric burning, stomatitis, diarrhea), which have been observed in about 25% of the patients, often are transient and can be minimized by giving the drug after meals and with milk at bedtime. These symptoms are severe enough to require discontinuing the drug in less than 10% of the patients but, even in these, the adverse effects may not recur when administration of the drug is resumed.

Indomethacin should be regarded as potentially ulcerogenic, although the available evidence on this point is contradictory. Some patients with a history of peptic ulcer have tolerated the drug without experiencing gastrointestinal symptoms or having evidence of an active ulcer; in other patients ulcers have developed after having taken the drug for 1½ to 3 years. Since most patients in whom ulcers had developed had received doses of 150 to 300 mg a day, dosage may well be a contributing factor. Occult bleeding and resulting anemia may occur in the absence of an ulcer; persistent indigestion may be a symptom of this. Although measurements indicate that the occult blood loss associated with indomethacin is less than that produced by clinically equivalent doses of aspirin, hemoglobin determinations should be made regularly and the drug should be discontinued if any evidence of gastrointestinal bleeding develops.

No significant hematologic reactions or alterations in the glucose-tolerance test, electrolyte balance, or liver and kidney function have occurred after administration of indomethacin for periods as long as three years. However, more long-term studies are needed to completely assess the effects of its prolonged use.

Other adverse effects reported infrequently are edema; psychic reactions such as depression; angioneurotic edema; drowsiness; tinnitus; blurred vision; and dermatologic reactions such as pruritus, urticaria, and rash. Indomethacin should be discontinued if these reactions occur. Leukopenia has been reported in a few patients.

PRECAUTIONS

Patients who require larger doses of indomethacin must be observed more closely for the possible occurrence of toxic effects. The patient may accept the untoward effects of indomethacin if he is told of their possible occurrence. Indomethacin, like aspirin, should be administered on a regular schedule and not used indiscriminately in the treatment of rheumatoid arthritis.

Although there is no definite evidence that indomethacin causes peptic ulcers, *it is contraindicated in patients with active ulcers*. In addition, because of its potential for causing bleeding in the gastrointestinal tract, the drug should be used with caution if there is a history of ulcer, regional ileitis, gastritis, or ulcerative colitis. Patients with these conditions may tolerate the drug if small doses are used. Indomethacin also should be used with care in patients who have epilepsy, parkinsonism, or emotional or psychiatric problems, since the drug may cause aggravation of these conditions.

Because of the possible occurrence of central-nervous-system effects, patients being given indomethacin should avoid activities requiring mental alertness, judgment, or physical coordination (e.g., driving a car, operating dangerous machinery), particularly during the early weeks of therapy.

No teratogenic effects have been demonstrated in animal studies. However, it has been shown that indomethacin does cross the placental barrier. Thus, the possibility of risk to the fetus must be weighed against the expected therapeutic benefits if indomethacin is considered for administration to a pregnant woman. Clinical studies have been insufficient to establish any recommendation for the use of indomethacin in *infants* and *children*.

PHARMACOLOGY

In man, indomethacin is absorbed promptly following oral administration, and peak plasma levels occur within two hours. About 90% of a single dose is excreted in 24 to 48 hours; approximately two-thirds of this amount is excreted in the urine as the glucuronide and the remainder is excreted in the feces.

DOSAGE AND PREPARATIONS

Route of Administration—Oral.

Dosage—To minimize adverse reactions, small doses of indomethacin are given initially; when necessary, the size of the dose is then gradually increased until an effective level is reached.

In *rheumatoid arthritis, ankylosing spondylitis*, and *degenerative joint disease of the hip*, the initial dose is 25 mg two or three times daily. If the patient does not respond, this dose is increased at weekly intervals by increments of 25 mg a day until a satisfactory response is obtained or until a daily dose of 150 to 200 mg is reached; larger doses are not recommended. If adverse reactions occur, the drug should be discontinued or successive adjustments in dosage should be made until the best possible response is obtained. After an acute phase or exacerbation of rheumatoid arthritis is controlled, the dose of indomethacin should be reduced to a satisfactory maintenance level. No reports on its occasional intermittent use for short periods are available.

When indomethacin is added to a regimen of corticosteroid therapy, it is often possible to reduce the dose of the steroid by as much as one half or to discontinue it entirely. However, this reduction should be made gradually in order to avoid the effects of steroid withdrawal.

Acute attacks of *gout* may be controlled with a dosage of 50 mg three times a day until the attack subsides. During the intervals between attacks, a dose of 25 mg twice a day may be sufficient.

Preparations—Capsules 25 mg.

Supplied by—Merck Sharp & Dohme (Indocin).

Year of Introduction—1965.

Generic and Trade Names of Drug

Phenylbutazone—*Butazolidin.*

[From Clin-Alert, June 15, 1966]

INDOMETHACIN—ACTIVATION OF LATENT INFECTION

No. 153

"In spite of the known tendency for anti-inflammatory compounds to cause flare-up of existing but controlled infection, there has been no previous report of this complication occurring with indomethacin (Indocin). Three patients are now described in whom indomethacin apparently reactivated infectious conditions. One patient developed pain and restricted motion of the right hip shortly after undergoing inguinal herniorrhaphy. X-ray examination showed a slight blurring of the outline of the femoral and acetabular articular surface but no actual bone destruction. While still under investigation for the hip condition the patient was inadvertently included in a group of patients to be treated with indomethacin. After receiving 100 mg. indomethacin daily for six days the patient suddenly became very ill, with excruciating pain in the hip. Bone destruction was evident on re-examination. Open drainage of the hip and synovial biopsy were carried out forthwith. Histological examination showed a granulomatous reaction consistent with tuberculosis and occasional acid-fast bacilli. Another patient sustained a hip fracture which was reduced by open operation. During the following four years the hip remained mildly painful. It was then decided to employ indomethacin, the drug being given in a dosage of 100 mg. daily. Dramatic symptomatic relief was obtained during the first three days but by the eighth day the patient was in greater pain than ever before. On admission to hospital the patient's condition was alarming. His temperature was 103°F, pulse 136, and classic signs of bilateral pneumonia were present. Blood culture produced a growth of Streptococcus aureus. Vigorous antibiotic therapy resulted in gradual improvement. The third patient had long-standing arthritis for which she had received steroids with disastrous effect—development of aseptic arthritis of the right hip joint. This occurred 5 years before being placed on indomethacin. After receiving the drug in a dosage of 100 mg. daily for 10 days the patient complained of severe pain and swelling of the left elbow. On examination she was found to have septic arthritis of the left elbow joint. Indomethacin was discontinued and antibiotic therapy instituted. Acute symptoms subsided within three weeks. It is suggested that the complications encountered in these patients were basically due to breakdown of local barriers to the spread of infection. This is a disquieting thought and calls for further investigation of the effects of indomethacin and greater care in the selection of patients for treatment with this drug which is currently being prescribed with considerable abandon."—Solomon (Johannesburgh, South Africa), British M.J. 1:961 (Apr. 16), 1966.

[Letters to the Journal]

[From Journal of the American Medical Association, Aug. 1, 1966, vol. 197, No. 5]

GENERIC AND TRADE NAMES OF DRUGS

To the Editor:—I should like to bring to your attention an error which, although probably typographical, is misleading, with possible serious consequences. In THE JOURNAL (196:651, 1966) is a discussion of "A Nonsteroidal Anti-inflammatory Agent: Indomethacin (Indocin)." At the end of the article under "Generic and Trade Names of Drugs" are listed "Phenylbutazone—*Butazolidin.*" Indomethacin and phenylbutazone are, of course, two separate drugs.

The dangers of prescribing phenylbutazone mistakenly when indomethacin is intended are obvious.

MARK N. MUELLER, M.D.

NEW HAVEN, CONN.

Because indomethacin (Indocin) was the subtitle of the Council Report, this was not included under "Generic and Trade Names of Drugs" at the conclusion. On the other hand, it is our custom to mention other drugs under "Generic and Trade Names of Drugs" if these have been discussed in the body of the communication. Phenylbutazone (Butazolidin) appeared on page 651. No one intended to imply that phenylbutazone and indomethacin were the same.

This is the first time such a confusion has been brought to the editor's attention.—ED.

[From Clin-Alert, Jan. 12, 1967]

INDOMETHACIN

[No. 3]

"Indomethacin (Indocin; Indocid-Merck Sharp & Dohme) can mask signs of infection and activate latent infection. Several deaths have been reported in children with severe forms of rheumatoid arthritis, dermatomyositis and rheumatic fever who were receiving indomethacin. Some of these children succumbed to intercurrent infection, the severity of which may have gone unrecognized during treatment. The role played by indomethacin in these cases is not known. However, it is recommended that *indomethacin not be used in children until results of further studies are available.*"—Chapman (Food & Drug Direct., Ottawa, Canada), Canad. M.A.J. 95: 1156 (Nov. 26), 1966

[Indomethacin is not a simple analgesic and should be used only in conditions for which it is currently recommended (rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, and gout). *Indomethacin should not be prescribed for children.* For additional information see manufacturer's recently revised literature.]

[Papers and Originals]

[From British Medical Journal, Jan. 14, 1967]

INDOMETHACIN IN RHEUMATOID ARTHRITIS: AN EVALUATION OF ITS ANTI-INFLAMMATORY AND SIDE EFFECTS

(By Phelim Donnelly,* M.D., M.R.C.P.I., D.Phys.Med.; Kenneth Lloyd,* M.R.C.P.; Hubert Campbell,† M.A., M.B., B.S.)

Since its introduction in 1963 indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid) has been reported as an analgesic of value in the treatment of osteoarthritis (Hart and Boardman, 1963; Wanka *et al.* 1964; Percy *et al.*, 1964) and ankylosing spondylitis (Katz *et al.*, 1963; Hart and Boardman, 1963; Smyth and Godfrey, 1964; Percy *et al.*, 1964; Rothermich, 1964; Michotte and Wauters, 1964; Boland, 1964), and as an agent that effectively reduces joint swelling and inflammation in acute gout (Hart and Boardman, 1963; Smyth *et al.*, 1963a, 1963b; Michotte and Wauters, 1964; Percy *et al.*, 1964; Norcross, 1963; Kåss, 1965). Similar though less striking results have been obtained with indomethacin in rheumatoid arthritis (Hart and Boardman, 1963; Norcross, 1963; Wanka *et al.*, 1964; Percy *et al.*, 1964; Catoggio *et al.*, 1964; Clark 1964; Rothermich, 1964; Datey, 1964; Smyth *et al.*, 1964; Thompson, 1964; Smyth, 1965; Thompson and Percy, 1966). Kelly (1964a, 1964b) found the benefit "often astonishing," while Boland (1964) was unable to demonstrate conclusively any effect of the drug on patients with rheumatoid arthritis. In the treatment of rheumatic fever Vignau *et al.* (1965) concluded that the advantages of indomethacin were outweighed by its side-effects.

A high incidence of side-effects in proportion to therapeutic effect with this drug in rheumatoid arthritis has been observed (Dixon *et al.*, 1963; Boland, 1964; Lövgren and Allander 1964; Percy *et al.*, 1964; Boyle, 1965). Percy *et al.* (1964) had to withdraw 13 out of 21 patients taking 200 mg. each day, and Katz *et al.* (1965) withdrew 35 out of 97 patients on doses of 100 to 400 mg. a day, for this reason. Hart and Boardman (1963) reported side-effects in 31 out of 52 patients on a daily dose of 50 to 300 mg. Rubens-Duval and Villiaumey (1964) reported 72% side-effects in patients on a daily dose of over 200 mg., and Robinson (1965) could maintain therapy in less than 50% of patients receiving 125 to 150 mg. a day. On the other hand, Robecchi *et al.* (1964), using doses of 75 to 150 mg. each day, had only one withdrawal with 28 patients and found that though side-effects were frequent they were not unduly troublesome. These findings indicate that the therapeutic index of this drug is low.

Hart and Boardman (1963) demonstrated no greater efficiency with the higher range of dose and recommended 50–150 mg. as a satisfactory daily dose of indomethacin consistent with minimal side-effects.

PRESENT TRIAL

This trial was designed (1) to test to analgesic and anti-inflammatory effects of indomethacin in rheumatoid arthritis over a short term in a relatively low dose, and (2) to note the true incidence of side-effects.

Patients were accepted for the trial on the basis of active inflammation of six or more proximal interphalangeal joints of the fingers. This criterion was specified because of the ease of measurement of swelling and tenderness of these joints. Patients with flexion deformity of the fingers or firm non-tender thickening of the proximal interphalangeal joints resulting from long-standing joint changes were excluded.

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Thirty patients with "classical" or "definite" rheumatoid arthritis were chosen (A.R.A. criteria, Ropes *et al.*, 1957). There were 18 women and 12 men, aged 28 to 72, average 52.6 years, with disease of six weeks to 24 years' duration, averaging 8 years 2 months. The duration of disease in nine was from six weeks to four years, in 12 from five to nine years, and in nine for 10 years or more.

A number of patients were already receiving long-term drug therapy, and the dose of these drugs was unaltered during the period of the trial. Six were receiving hydroxychloroquine 600 mg./day, one was receiving oxyphenbutazone, and one Thylin (nifenazone). Adrenocorticosteroids had been given for the previous two years to two patients. One patient on weekly injections of 50 mg. of gold had received a total of 550 mg. of Aurothiomalate at the time of entry into the trial.

DESIGN

The trial lasted for ten weeks, including a "pre-trial" week at the beginning of which an assessment was carried out in order to accustom the patients to the trial procedure; these measurements were discarded. During this week two capsules of placebo were administered—a fact known to the examiner but not to the patient—with the intention of minimizing any placebo response by the time of entry into the trial proper at the end of this week when the first recorded assessment was carried out.

After this week the trial began, a double-blind crossover technique being used over two four-week periods, separated by a week during which all patients received two capsules a day of the placebo. The second placebo week was intended to minimize any possible "carry-over" effect of the drug into the placebo weeks in the group who received the active drug initially.

Indomethacin in standard commercial 25-mg. capsules was matched by a similarly coloured placebo powder (mainly lactose) in identical capsules sealed in similar containers. Two separate dose sequences were prepared. Patients in group 1 received indomethacin first for four weeks, followed by placebo for a further four weeks; those in group 2 received placebo followed by the drug. An incremental dosage scheme was adopted in order to reduce the incidence of side-effects (Hart and Boardman, 1963, 1964; Suzman, 1964; Dilsen and Dilsen, 1964; Thompson, 1964). Each four-week period began with two capsules a day. The dose was then increased by one capsule a day at the beginning of each of the ensuing three weeks. Thus, when indomethacin was administered the patients received a daily dose of 50 mg., 75 mg., 100 mg., and 125 mg. respectively during each of the four consecutive weeks (Fig. 1).

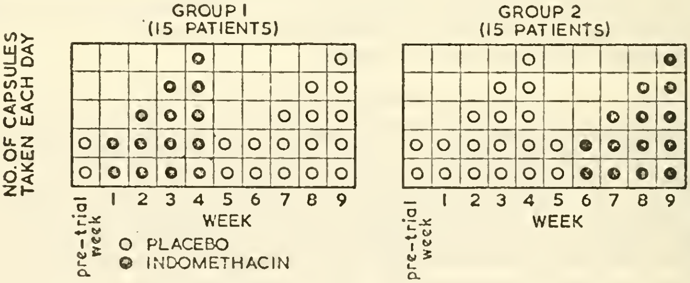

Figure 1.—Dosage scheme of trial.

The patients were instructed to swallow the capsules with fluid, during or immediately after a meal, and were requested to return the container with any remaining capsules each week in order to receive their supply for the following week.

The first 30 patients examined in the outpatient clinic who fulfilled the criteria of the trial were accepted. They were numbered 1 to 30 consecutively as they entered the trial, each number having previously been allocated at random to either group of 1 or 2.

ASSESSMENTS

Weekly assessments were carried out, the following criteria being used: (1) hand articular index, (2) pool finger swelling, (3) systemic index(Lansbury, 1958), and (4) patient's opinion.

Hand articular index

The amount of small joint involvement of the hands was assessed by the presence of tenderness on firm palpation of the proximal interphalangeal and metacarpophalangeal joints, no attempt being made to grade the degree of tenderness present. The result was expressed as a sum of the number of joints so affected, the maximum possible being 20.

Pool of finger swelling

The degree of swelling of each proximal interphalangeal joint was recorded with jeweller's ring-gauges. These consist of a collection of 52 rings of graded sides from the smallest labelled "A" through "A½," "B," "B½," to the largest "Z½." The circumference of all eight proximal interphalangeal joints and of the two thumb terminal joints, whether affected by arthritis or not, was determined by the smallest ring that could be passed over each joint. The letter size of the rings was equivalated numerically from 1 to 52; swelling too large to accommodate the largest ring was recorded at "53." Therefore the sum of the measurements of these 10 joints allowed a theoretical maximum score of 530.

Systemic index

This index was devised by Lansbury (1958) as a composite numerical expression of five characteristics of rheumatoid arthritis and is used as an indicator of activity of the disease. Its compilation utilizes five factors: (1) number of analgesic tablets taken each day, (2) duration of morning stiffness, (3) onset of fatigue, (4) strength of hand grip, and (5) E.S.R. (Westergren).

1. Patients were instructed to continue to take any analgesic tablets (usually asperin) that they had already found effective and tolerable, but they were to regulate the dose and frequency of these tablets according to the demands of the pain. Put simply, "no pain, no tablets; much pain, many tablets; little pain, few tablets." This instruction was repeated each week and the patients were asked to record or remember the number of tablets taken daily, or the number per dose and the frequency of administration.

2 and 3. Patients were asked to note the duration of body stiffness after rising each morning and the length of time elapsing before the onset of fatigue every day.

4. Strength of grip was measured by using a folded rectangular rubber bag in a fabric cover measuring 12 by 6 cm. when deflated. This was connected to a sphygmomanometer recording to 300 mm. Hg and inflated to a pressure of 20 mm. Hg with the valve closed. The height sustained by a single maximum-effort squeeze with each hand was recorded as the mean for both hands. Adequate rehearsal of the method was given at the pretrial examination.

Each of these estimations was accorded a number as indicated by reference to the standard table of Lansbury and the systemic index expressed as the sum of these numbers; the higher the number the more active is the arthritis.

Patient's opinion of the effectiveness of the capsule

This was judged by their general well-being and their feeling as regards their "rheumatic" symptoms over the week preceding. They were requested to express this as either "much better," "better," "no change," "worse," or "much worse." This was recorded each week as "+2," "+1," "−1," or "−2" respectively. In addition, at the end of the trial the patients were asked their opinion of the capsules and whether they wished to continue taking them.

In addition, on entering and leaving the trial two further assessments were carried out:

Functional grade.—Grades 1–5 were used as recommended by the Joint Committee of the M.R.C. (1954).

Articular Index.—This is a means devised by Lansbury to express numerically the total area of joint inflammation as indicated by tenderness or pain on passive movement. Joints are graded according to size and allocated appropriate numbers: the larger the joint the higher the number: the higher the index the more extensive the arthritis. Thus comparison of total scores indicates expansion or contraction of the pool of joint inflammation.

These estimations entailed 2.740 separate observations which were made by one of us (P. D.) with the exception of 168 observations made over one two-week period.

SIDE EFFECTS

The incidence and nature of side-effects were recorded weekly. Great care was taken not to inform the patients of any specific side-effects that might be expected, and they were not asked to report any untoward feelings or occurrences. No direct questions were put in this matter: the recorded side-effects were all elicited as a result of spontaneous remarks by the patients in the course of conversation about their general health and well-being.

Routine urine examination, haemoglobin estimation, and total white cell and differential counts were performed weekly. Serum albumin and globulin levels and electrophoretic differentiation, as well as thymol turbidity, flocculation, serum bilirubin, alkaline phosphatase, and glutamic and oxaloacetic transaminases, were performed at the conclusion on all patients completing the trial.

During the course of this trial Bruckner and Randle (1965) reported hepatotoxicity associated with the use of indomethacin. Because of this, further toxicity studies were extended beyond the trial period on those patients who continued taking indomethacin, and will be the subject of a separate communication.

RESULTS

Twenty-eight patients completed the trial. Two patients were withdrawn; one as as result of side-effects which were found to be associated with the placebo and one because of irregular attendance.

Although there was a strict random allocation of patients to groups 1 and 2, these two groups were not comparable during the control period. Those who were given the placebo before the indomethacin were more severely affected by rheumatoid arthritis than were those who were treated with indomethacin first and given the placebo subsequently.

The score by the systemic index of group 1 was 55 during the control period and for group 2 was 71, a difference of 16 units. This difference persisted throughout the trial, so that at the end of it group 1 had a mean systemic index of 44 units and group 2 of 57 units. Fortunately, there was a full range of all grades of patients in both groups; in group 1 the range of scores for the systemic index during the control period was from 73 units to 19 and in group 2 from 117 to 18.

A similar difference between these two groups could be shown for each of the indices used as a measure of disease. For all indices except one, group 2 was more severely affected than group 1 during the control period and remained so throughout the trial period.

Articular index

A change of 10 or more in the articular index at the completion of the trial compared with the admission figure was taken to indicate either spread or regression of the arthritis.

Of the 28 patients 11 had a smaller index on completion, in nine it increased, and in eight there was no change. The timing of active therapy did not appear to affect this result. Of the 14 patients who received indomethacin in the last month one showed no change, six were worse, and seven better, as judged by the articular index.

1. Hand articular index

This is a measure of the patients' response to pain as well as the extent of the pain experienced. Both groups of patients showed a reduction of sensitivity to squeezing of finger joints during the course of the trial, and the rate of regression in the response to this procedure was the same for both groups irrespective of whether they were on the drug or on the placebo.

During the month on placebo the average number of painful joints for all patients was 9.2, whereas during the month on indomethacin the average was 9.5 joints affected, a completely negligible difference (see Statistical Tables).

The number of patients who were better during the month on placebo was 15; 12 were better during the month on indomethacin and one was unchanged.

There was no evidence of any "carry-over" effect during the first two weeks after the use of indomethacin, nor was there any evidence of deterioration during the period on the placebo.

2. Pool of finger swelling

The use of jewellers' ring-gauges helped to eliminate the subjective response: none the less, there was a marked improvement in both groups of patients over the period. This may have been due partly to increasing patient-tolerance to the rings and partly to the physician's increase in pressure when applying the rings.

Both groups responded in the same way on indomethacin. Group 1 improved slightly during the month and then continued to improve when placed on the placebo, and group 2 responded slightly on the placebo but continued to respond when treated with the active principle. Fifteen patients did better during the month on the placebo, whereas 13 did better on the indomethacin. The net result was that the mean score for both groups was identical at 366 units per patient. None of these differences are of formal statistical significance (see Statistical Tables).

Patients were selected for the presence of inflammatory fingerjoint swellings. As some of these swellings were too large for measurement by the standard range of jewellers' ring-gauges, they were recorded as "53." Consequently, it was not possible to record fluctuations in their size. Accordingly, this factor would tend to reduce the amount of shift recorded in the pool of finger swelling. This point was examined by taking the six patients with a pool of finger swelling of "500" or over and comparing them as a group with the remaining 22 patients.

It was confirmed that though the contraction of the pool of swelling was less marked and the rate of improvement less steep in the group with the larger swellings the overall trend of this and the other measurements did not differ. Accordingly, this factor did not significantly affect the results.

3. Systematic Index

(i) *Analgesic Tablets.*—Group 1 showed a decline during the period of treatment with a relapse when this was changed to a placebo, whereas there was no difference at all in the habits of group 2, who were rather more severely affected by the disease and were using more tablets. The mean difference between the two periods was negligible (see Statistical Tables). Fifteen patients took more tablets during the treatment period and 11 more during the placebo period; two remained unchanged.

(ii) *Duration of Morning Stiffness.*—This showed no consistent trends. Ten patients felt that they had improved during the treatment and 10 during the placebo period. Eight were the same during both months (see Statistical Tables).

(iii) *Fatigue.*—The delay in onset of fatigue suggests that indomethacin has some important "tonic" effect, but it is interesting to note that in this test alone group 1 was worse than group 2 during the control period. Group 1 rapidly improved on indomethacin and relapsed again on placebo, whereas group 2 grew worse on the placebo and improved on the drug. The overall effect was that the mean delay in fatigue was 5.9 hours on indomethacin and 5.1 hours on the placebo; this difference is not statistically significant (see Statistical Tables). Thirteen patients thought they were less fatigued during the treatment month and seven during the placebo month: eight detected no difference.

(iv) *Hand Grip.*—The ability to squeeze the bag improved with practice, and once again there was evidence of a "learning" effect in the changes. Group 1 was consistently better than group 2, but group 1 improved rapidly on indomethacin but failed to continue this improvement on placebo, whereas group 2 improved on the placebo and continued to improve on the drug. The net result was that the mean grip during indomethacin was 189 mm. Hg and during the month on placebo was 185, a difference of 4 mm. Hg to the advantage of indomethacin (see Statistical Tables). Sixteen patients were better during the period on indomethacin and 12 during the placebo period.

(v) *Erythrocyte Sedimentation Rate.*—The E.S.R. is the only measurable variable that is no influenced by subjective feeling or observer error. The two groups were initially quite different from each other; group 1 had an E.S.R. of 55 mm. and group 2 of 71 mm., a difference of 16 mm. When group 1 was started on the drug there was an increase in the E.S.R., and when the placebo replaced it there was a sharp fall. Similarly, group 2 improved while on the placebo, but as soon as the drug was used the E.S.R. increased once again to a level higher than that during the control period. During the treatment period the mean rate was 48.6 mm. and during the placebo period it was 42.4 mm., a difference of 6.2 mm., with a standard error of 3.8 (t=1.8 P=0.1). Though the difference does not reach a formal statistical significance, the consistency of the pattern suggests that in fact indomethacin has an action to increase the E.S.R. (see Statistical Tables). Seven patients improved during the month on indomethacin and 21 during the month on placebo.

The *Systemic Index* is arrived at from aggregation of the results of the above five methods of measurement. It is already clear that there were no important differences. However, the systemic index was much higher in group 2 than in group 1, but both groups of patients improved steadily during the period of the trial. The mean score of the 28 patients during their month of treatment was 54.4 and during the month on placebo was 55.7, a difference of 1.3±4.0—a difference which is not statistically significant (see Statistical Tables). Sixteen patients were better during the treatment month, 11 during the placebo month, and one was unchanged.

4. Subjective Opinion

Almost all patients felt that they had benefited by the treatment during the period of the trial. 13 thought they were better during the month on indomethacin. 13 preferred the month on placebo, and two were unable to distinguish the two periods (Fig. 2).

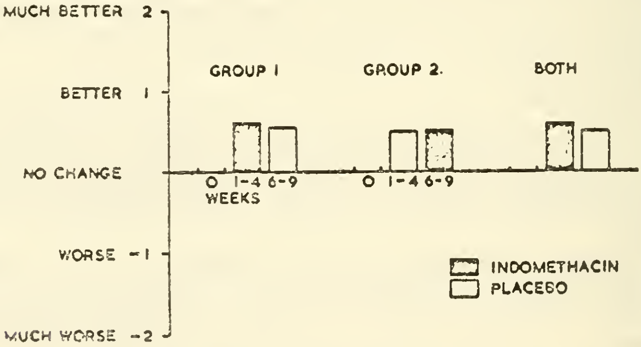

FIGURE 2.—Subjective opinion.

5. Functional Grade

There were no significant differences here, and the results are set out in Table I.

The inclusion of patients with long-standing disease did not affect the results: extraction of these results and comparison with the remaining patients and with those having disease of short duration showed no difference.

All the results have been reported as an average of four examinations during the month on indomethacin compared with a similar average while on a placebo. No substantial difference to any of the conclusions was made when the results for the fourth examinations alone at the end of each four-week period were compared with each other. The trends of the various responses during these two periods appeared to be similar, and hence should be attributed to some cause other than specific drug action.

TABLE

Functional grade		Entering trial—					
		I	II	III	IV	V	Total
Leaving trial	I	17	1	0	0	0	18
	II	0	2	3	0	0	5
	III	1	0	3	0	0	4
	IV	0	0	0	1	0	1
	V	0	0	0	0	0	0
Total		18	3	6	1	0	28

SIDE EFFECTS

The commonest side-effects were headache and gastrointestinal upset. Though the incidence was equal for both indomethacin and placebo, the frequency was higher with indomethacin.

Side-effects occurred in 18 (60%) of the 30 patients while taking indomethacin and in 17 (56.7%) while taking placebo. In 9 (30%) patients side-effects were reported with both placebo and indomethacin, in 10 (33.3%) when taking placebo only and in 11 (36.6%) with indomethacin alone. These are itemized in Table II.

TABLE II.—SIDE-EFFECTS

Type of side effect	Patients affected		Weeks affected	
	Indomethacin	Placebo	Indomethacin	Placebo
C.N.S	13	14	20	16
Headache	8	8	15	8
Sleepiness	3	1	3	3
Depression	1	2	1	2
Giddiness	1	2	1	2
Muzzy head	0	1	0	1
G.I.T	16	12	25	14
Dyspepsia	5 }12	3 }12	6 }20	4 }14
Nausea	3	5	10	5
Anorexia	1	1	1	2
Vomiting	3	3	3	3
Diarrhoea	2	0	3	0
Activation of D.U	1	0	1	0
Activation of hiatus hernia	1	0	1	0
Miscellaneous	10	8	12	11
Rash	2	1	3	2
Increase of arthralgia	2	1	3	2
Neck stiffness	1	2	1	2
Thrombophlebitis	1	1	1	1
Stroke	1	0	1	0
Fatigue	1	0	1	0
Scleral injection	1	0	1	0
Faint feelings	0	1	0	1
Excess sweating	0	1	0	2
Muscle weakness	1	1	1	1

One patient in group 2 withdrew from the trial because of severe side-effects which occurred during the first week of placebo administration. One man with duodenal ulcer and one woman with hiatus hernia, both diagnosed radiologically before the trial, experienced recurrence and worsening of dyspeptic symptoms while on indomethacin.

The occurrence of thrombophlebitis in one man on indomethacin was matched by a similar occurrence in one woman receiving placebo. Both had a previous history of thrombophlebitic episodes.

Transient loss of power in one arm was reported by a man with hypertension after receiving indomethacin 50 mg./day for two days. Rapid improvement occurred and no further episodes were observed, though indomethacin was continued. Cerebral vascular accidents have been recorded previously in patients on indomethacin (Coste *et al.*, 1964).

STATISTICAL TABLES

Mean Scores and Standard Error of Mean.—The mean scores during the control period were based on one reading from each patient, and the mean scores during the treatment and placebo periods were based on four readings from each patient.

The difference is taken in every case, so that a plus sign indicates that the patients were better on indomethacin, a negative sign that they were better on the placebo. Group 1: 14 patients treated with indomethacin followed by placebo. Group 2: 14 patients treated with placebo followed by indomethacin.

Group	Control period	Indomethacin	Placebo	Difference
HAND ARTICULAR INDEX—NUMBER OF JOINTS PAINFUL				
Group 1	11·9	9·6±0·9	7·6±0·9	−2·0±1·3
Group 2	12·7	9·4±0·8	10·7±0·8	+1·3±1·1
All patients	12·3	9·5±0·6	9·2±0·6	−0·3±0·9
POOL OF FINGER SWELLING—SUM OF JEWELERS' RING-GAGES PASSED OVER THE FINGER				
Group 1	374	366±10	349±10	−17±14
Group 2	388	366±10	383±10	+17±14
All patients	381	366±7	366±7	0±10
USE OF ANALGESIC TABLETS—NUMBER OF TABLES USED DAILY TO RELIEVE PAIN				
Group 1	5·9	4·3±0·5	4·8±0·5	+0·5±0·7
Group 2	7·5	7·5±0·7	7·6±0·8	+0·1±1·0
All patients	6·7	5·9±0·4	6·2±0·5	+0·3±0·6
MORNING STIFFNESS—DURATION IN HOURS UNTIL STIFFNESS RELIEVED				
Group 1	1·9	1·9±0·35	2·0±0·43	+0·1±0·56
Group 2	2·0	2·0±0·34	2·0±0·23	0·0±0·41
All patients	1·9	2·0±0·24	2·0±0·24	0·0±0·35
DURATION OF FATIGUE—HOURS UNTIL ONSET OF FATIGUE[1]				
Group 1	4·5	6·0±0·6	5·2±0·6	+0·8±0·8
Group 2	5·9	5·8±0·6	4·9±0·5	+0·9±0·8
All patients	5·2	5·9±0·4	5·1±0·4	+0·8±0·6
HAND GRIP—PRESSURE (MM. HG) IN SPHYGMOMANOMETER BULB[1]				
Group 1	164	196±9·5	195±9·1	+1±13
Group 2	153	183±10·4	176±9·3	+7±14
All patients	158	189±7·1	185±6·5	+4±10
ERYTHROCYTE SEDIMENTATION RATE. MM. (WESTERGREN)				
Group 1	44·7	46·1±4·0	39·5±3·7	−6·6±5·5
Group 2	49·1	51·0±3·3	45·3±3·6	−5·7±5·1
All patients	46·9	48·6±2·7	42·4±2·6	−6·2±3·7

[1] An increase in this score means the patient has improved.

SYSTEMIC INDEX—UNITS

Group	Control period	Indomethacin	Placebo	Difference
Group 1	55	48·9±3·0	48·2±3·8	−0·7±4.8
Group 2	71	59·8±4·2	63·2±4·7	+3·4±6·3
All patients	63	54·4±2·6	55·7±3·0	+1·3±4·0

DISCUSSION

This trial differs in three important respects from all trials previously reported. Two of these concern modifications to the standard double-blind crossover techniques.

1. The placebo effect that often occurs early during the administration of any drug was diminished by the addition of a pretrial week of placebo only. As a result the baseline figures obtained at entry and used for subsequent comparison, though smaller, were more accurate.

2. Another week of placebo administration was inserted at the crossover in order to minimize dilution of meaurements, early in the placebo month, by carry-over of drug response in those patients receiving the drug first.

3. The incremental dose schedule was fixed, and remained unaltered despite the occurrence of side-effects and apparent therapeutic response.

In many of the previously reported trials the dose of indomethacin was permissive, depending on the above factors, with consequent variation in the maximum daily dose achieved in the individual patient, varying from 75 to 300 mg.

In a somewhat similar trial Ward (1964), using indomethacin 200 mg./day in tablet form, demonstrated improvement in morning stiffness and joint tenderness but no change in finger swelling (measured by ring size), grip strength, or in the patients' assessment of pain. In a subsequent double-blind (but *not* crossover) trial, using 150 mg./day in capsule form, he confirmed the above findings except that pain was lessened, and an additional measurement of swelling of larger joints (estimated by eye) was said to show improvement by indomethacin. Thus his claim for beneficial effects was based on subjective measurements only.

Within the dose and time limitations of our trial there was no indication of any anti-inflammatory, detumescent, or analgesic effect of indomthacin on patients with rheumatoid arthritis that could be detected statistically by the eight criteria used.

Two measurements remained unchanged throughout the 10 weeks of the trial—duration of morning stiffness and patients' opinion. Four others showed changes that could not be regarded as significant.

Only two of the criteria used were affected by indomethacin—E.S.R. and time to onset of fatigue—though the changes demonstrated did not reach the level of formal statistical validity.

The delay in onset of fatigue, without other evidence of improvement, was quite noticeable. Many of the patients reported considerable increase in the amount of physical activity they were able to undertake. This effect of indomethacin has not been previously reported. The rise in E.S.R. has been reported—Miehlke (1965) found an increase in 21 out of 53 rheumatoid patients who were on indomethacin, and Rubens-Duval and Villiaumey (1964) reported raised E.S.R. in some patients. Persistence of an already elevated E.S.R. despite clinical improvement has been noted by Viara and Marrazzi (1964), Katz *et al.* (1965), and Robecchi *et al.* (1964). The mechanism of this E.S.R. rise is obscure and is being investigated.

An important practical point emerges: in patients with rheumatoid arthritis receiving indomethacin it would seem that the E.S.R. can no longer be regarded as a reliable indicator of disease activity.

The two most important clinical indicators of inflammation used in this trial were the hand index and pool of finger-joint swelling. Both of these showed systematic improvement throughout the course of the trial, suggesting that the factors influencing these changes were the results of learning and placebo rather than the expression of any pharmacological effect that could be attributed to indomethacin. These improvements were not the result of changes to be expected in some patients attending for the first time after a recent onset or exacerbation of arthritic disease. All patients, with one exception, were selected from the regular panel of the follow-up clinic, from patients with fixed review appointments.

This general placebo response was borne out by the patients' opinion of the effect of the capsule: 24 of the 28 patients completing the trial elected to continue taking indomethacin capsules even though only 14 were actually receiving the drug at the time of their decision.

There was no evidence of any decrease in joint pain within two or three days, but we did confirm the measurable reduction in finger-joint swelling reported by Hart and Boardman (1963) with doses varying from 50 to 100 mg.; we have demonstrated that this is a learning effect. Katz *et al.* (1963) noted a therapeutic response within 24 to 48 hours, and Ballabio *et al.* (1963), administering doses of indomethacin as low as 100 mg./day, claimed to show anti-inflammatory effects in rheumatoid arthritis within a few hours of administration. We failed to confirm this. Neither did we find evidence of the rebound exacerbation associated with sudden cessation of indomethacin treatment experienced by other workers (Katz *et al.*, 1965).

The use of an "all-or-none" response to digital pressure applied by the assessor as an indication of joint tenderness was thought to be a more accurate measurement for assessing inflammation at weekly intervals than grading the response. It was thought that, even with the same physician taking the measurements, it was impossible to apply the same pressure at weekly intervals with sufficient accuracy to make grading of any value.

We failed to show any analgesic effect of indomethacin, as judged by a fall in the number of analgesic tablets taken each day. The apparent beneficial effect demonstrated in group 1 was offset by the lack of response in group 2, who had the more severe disease. No conclusion can be made from these results. Despite repeated instruction that analgesic tablet dose was to be related to the degree of arthralgia some patients were reluctant "to take tablets." Others, particularly those in group 2, were disinclined to alter a long-established rigid dose-scheme of analgesic tablets. On the other hand, incidental discomfort, not related to the arthritis, as with coryza, influenza, headaches, and even side-effects of the drug, affected the number of aspirin tablets taken by those who carried out their instructions precisely. Of all the measurements used it was thought that this was the least reliable.

With adequate time spent on explanation and rehearsal, our method of measurement of grip strength was accurate enough to justify its substitution for the more time-consuming method suggested by Lansbury (1958). A pretrial comparison of these two methods showed very little difference.

The patients' opinion of the effectiveness of the capsules was found to be a subjective and unreliable indicator on which to base a judgment. In addition to the "normal" clinical variation in feeling of well-being and mood, the incidence and type of side-effects associated with the use of the capsules obviously influenced the patients' opinion. It was also found that the expressions "worse" or "much worse" could apply to the day of assessment or to the previous day, rather than to the week as a whole; the patients' memory of their feelings over the previous week tended to be influenced by their immediate feelings on the day of examination.

The systemic index of patients receiving indomethacin would have shown improvement on this trial were it not for the rise in E.S.R. On the other hand, any fall in the index would then have been due entirely to the effect of the indomethacin in delaying the onset of fatigue; for the other three measurements—grip strength, dose of analgesic tablets, and duration of morning stiffness—remained unaffected.

We took great care to avoid suggesting side-effects to our patients, but in spite of this symptoms occurred with approximately equal incidence during drug and placebo administration and followed a similar pattern in both groups. However, the frequency was greater with indomethacin, notably as regards headache and gastrointestinal upset. It is worthy of note that the only patient withdrawing from the trial developed headache, nausea, anorexia, and skin rash after receiving only placebo for four weeks. This picture indicates that suggestion did in fact play a large part in producing side-effects. We could not eliminate cross-chat in the waiting-room between patients in the trial and also between other patients taking indomethacin outside the trial.

A high placebo response is a well-recognized feaure in patients attending a rheumatological clinic, and this high level of placebo response implies susceptibility to other forms of suggestion; our results support this. This seems to indicate that the true incidence of side-effects attributable to the drug is very much less than 50 to 70% recorded here and in other papers. We regard the

37% of patients who developed side-effects on indomethacin alone as a more realistic estimate, but even this figure may be an exaggeration, for 30% experienced similar side-effects while receiving placebo.

SUMMARY

In a double-blind crossover clinical trial occupying 10 weeks indomethacin was given in capsule form for four consecutive weeks, starting with a daily dose of 50 mg. and increasing by one 25-mg. capsule a week to a maximum of 125 mg./day. The results on 30 patients with classical or definite rheumatoid arthritis are tabulated and discussed.

With the criteria of assessment based on the systemic index and articular index of Lansbury and measuring finger-joint swelling by means of jewellers' ring-gauges it was not possible to show that indomethacin produced any antiphlogistic effect that held statistical validity. The detumescent and analgesic effects demonstrated were shown to be the result of placebo and learning factors.

A tendency for indomethacin to accelerate the rate of erythrocyte sedimentation was revealed, and evidence for a specific anti-fatigue effect of the drug in rheumatoid arthritic patients is presented.

Side-effects are listed. Though they occurred more often with indomethacin, the incidence, type, and pattern were the same with both drug and placebo. The inference is made that suggestion played a part in determining both the incidence and the variety of side-effects encountered in the trial.

Compilation of our findings was considerably assisted by computer analysis of the figures; our thanks are due to Messrs. Merck Sharp and Dohme Ltd. for a grant to defray the expenses of this, also to Dr. Robert Hodgkinson, of the same firm, for his advice, for supplying the placebo and indomethacin capsules, and for arranging the randomization.

Our thanks are also due to the staff of the pathology and pharmacy departments of the Cardiff Royal Infirmary; to our secretaries and the medical illustrators who were so helpful; and to Nurse Jenkins of our outpatient department, who assisted in the weekly clinics.

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[From the Journal of the American Medical Association, Feb. 20, 1967, vol. 199, No. 8, pp. 586–587]

Fatal Hepatitis Probably Due to Indomethacin*

(By Weston M. Kelsey, M.D., and Modesto Scharyj, M.D.)

(Fatal toxic hepatitis developed in a 12-year-old boy while receiving indomethacin (Indocin))

REPORT OF A CASE

This 12-year-old Negro boy (NCBH 39–32–27) was first seen at the North Carolina Baptist Hospital at the age of 11 years, because of severe juvenile rheumatoid disease of undetermined duration. Although he had severe deforming arthritis at that time, the precipitating cause for admission on July 7, 1964, was severe anemia. The presence of many hypersegmented polymorphonuclear leukocytes, an increased excretion of formiminoglutamic acid, and his response to folic acid suggested a folic acid deficiency. His bilirubin level was 0.2 mg/100 ml and his cholesterol value was 141 mg/100 ml. Treatment with prednisone was instituted since he was in so much pain that attempts at physical therapy failed. The activity of his disease decreased so that ambulation became possible. He was discharged on July 24, 1964.

On January 5, 1965, his sedimentation rate was normal and his electrophoretic pattern had reverted from one showing marked hypergammaglobulinemia to a normal pattern.

He was admitted to an orthopedic hospital in October 1965, for operative procedures on his hips. No jaundice was noted and the liver was palpable at the costal margin. The disease again became active, with so much fever and pain that reinstitution of steroid therapy was necessary. His symptoms persisted so that he was given 100 mg of indomethacin daily, 2.5 mg/kg/day. Review of his hospital record revealed that he received no transfusions until the terminal episode. The only drugs he received were prednisone, a brief course of therapy with aspirin, and indomethacin. Hepatitis had not been reported in the hospital population. During this hospitalization his general status did not change until the terminal illness. In spite of the combined steroid and indomethacin therapy, his disease remained active so that operative procedures had to be postponed. On May 13, 1966, he had profuse rectal bleeding. On May 16, 1966, scleralicterus was noted. His total bilirubin at that time was 23.3 mg/100 ml. His prothrombin time was 19.6 seconds, with a control of 13 seconds. He was given 2 units of whole blood and then referred to the North Carolina Baptist Hospital.

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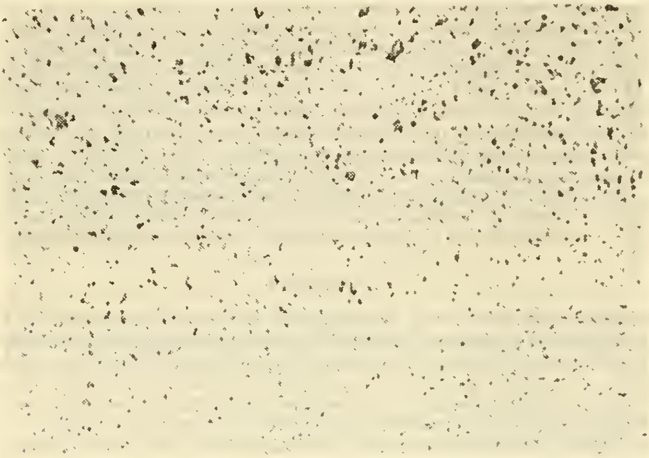

FIGURE 1.—Centrolobular necrosis and absence of inflammatory cells (hematoxylin and eosin ×45).

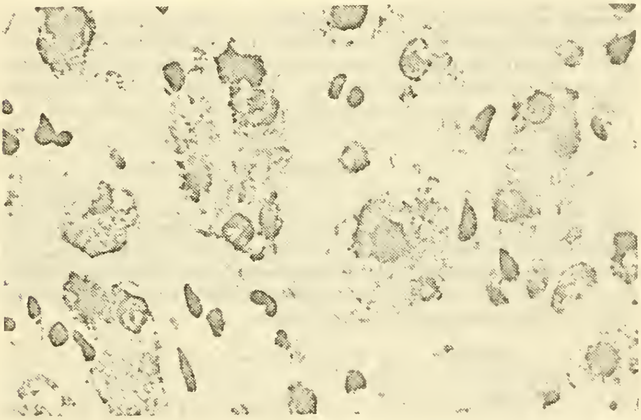

FIGURE 2.—Intracytoplasmic vacoules representing small lipid droplets in the preserved parenchymal cells adjacent to area of necrosis (hematoxlyin and eosin, ×400).

On admission he was critically ill. There was profuse rectal bleeding. He was markedly jaundiced. The liver was palpable 2 fingerbreadths below the right costal margin and was tender. There was obvious acute arthritis.

Laboratory tests disclosed the following results and values: urinalysis, normal; hemoglobin, 15 gm/100 ml; white blood cell count, 38,000 with 92% segmented neutrophils and 4% band forms: blood urea nitrogen, normal; total bilirubin, 28.8 mg/100 ml with a direct bilirubin of 12.6 mg/100 ml; serum glutamic oxaloacetic (SGOT), 242 units and the serum glutamic pyruvic acid, 100 units; cephalin flocculation, 3+; prothrombin, 14.8 seconds with a control of 12 seconds. Numerous blood cultures were sterile.

During his ten-day stay in the hospital he was too sick to institute satisfactory studies of his gastroinstestinal tract, or perform surgery. He received 22 units of blood in an attempt to maintain his blood volume. The bilirubin value gradually rose to a total of 50.4 mg/100 ml, with the direct bilirubin being 28 mg/100 ml. The SGOT level rose to 1,518 units. He died on the tenth hospital day.

Postmorten Examination.—The postmorten examination revealed jaundiced sclerae, and petechial hemorrhages in the lungs, trachea, heart, renal pelves, mucosae of the urinary bladder, and the intestinal tract. There was 1,200 ml of ascitic fluid. The liver was markedly enlarged and weighed 1,465 gm. The spleen weighed 250 gm. and the kidneys were 180 and 205 gm. respectively. Microscopic changes in the liver (Fig. 1 and 2) were characteristic of an acute toxic hepatitis, as described by Popper and Franklin.[1] There was central lobular zonal necrosis with fatty metamorphosis of a small-droplet type. Neither hyalinized cells nor evidence of parenchymal regeneration was present. Bile thrombi were numerous and inflammatory changes were minimal. It was felt that the above changes corresponded with the combined cytotoxic and cholestatic type of a drug-induced liver disease, according to Smetana's classification.[2] The findings in the remaining organs were interpreted as splenic passive hyperemia and cholemic nephrosis.

COMMENT

Indomethacin has now been widely used in the management of rheumatoid disease in adults. While many studies have been done looking for hepatotoxicity, this author is unable to find a documented toxic hepatitis due to this drug, either in an adult or a child. However, the advertisements concerning the use of this drug warn about this possibility by reference to transient elevations in alkaline phosphatase, cephalin-cholesterol flocculation, thymol turbidity, and SGOT values. In a personal communication to the authors, the manufacturer reported no cases of proven hepatotoxicity. The case of one child, somewhat similar to that of the present patient, has been reported to the manufacturer, but because of inconclusive data, has not been published in the medical literature. This case was not as clearly cytotoxic as the present one and the presence of infectious hepatitis could not be excluded.

While studies of toxicity of indomethacin in immature animals and children are in progress, no results are yet available in the literature.

Although it can not be proven beyond doubt that the cytotoxic agent responsible for this case of fatal hepatitis was indomethacin, no other drug could be incriminated. Since one other unreported case similar to this one is known, it is suggested that the use of the drug in children be associated with careful observations of liver function.

SUMMARY

Death, possibly due to indomethacin, occurred in a 12-year-old boy. It is important that practitioners should adhere to the manufacturer's recommendations that the drug should not be administered to pediatric age groups until the indications for usage and dosage have been established. Investigative studies on pediatric patients are currently being conducted, and until these studies are completed, indomethacin is not recommended for children.

Generic and Trade Names of Drugs

Indomethacin—*Indocin.*
Prednisone—*Deltasonic, Deltra, Meticorten, Paracort, Cotone, Lisacort, Metasone.*

[From Wall Street Journal, Mar. 14, 1967]

SLOPPY RESEARCH: DOCTORS, FIRMS FAULTED FOR CARELESS EVALUATION OF DRUGS, TECHNIQUES—ARTHRITIS PRODUCT'S EFFICACY QUESTIONED; A TREATMENT FOR ULCERS NOW IN DOUBT—SOME RESEARCHERS PENALIZED

(By William M. Carley, Staff Reporter)

NEW YORK.—In 1965 Merck & Co. introduced a new drug that it claimed was highly effective against rheumatoid arthritis. According to Merck, the drug, called Indocin, produced "improvement" in 50% to 80% of the arthritic patients on whom it was tested, reducing pain, stiffness, swelling and tenderness. It also produced a big jump in Merck's sales and profits last year.

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[1] Popper, H., and Franklin, M.: Viral Versus Toxic Hepatic Necrosis, *Arch Path* 46: 338–375 (October) 1948.

[2] Smetana, H. F.: The Histopathology of Drug-Induced Liver Disease, *Ann. N.Y. Acad. Sci.* 104: 821–846, 1963.

But a committee of physicians specializing in arthritis recently blasted much of the clinical research on which Merck based its claims. In a report appearing in a medical journal, the panel asserted that many of the doctors who evaluated Indocin for Merck conducted their investigations in such slipshod fashion as to make their conclusions extremely suspect. The committee did not look into Merck claims that Indocin is useful in treating certain other diseases, but it said its own research indicated that Indocin was no better than ordinary aspirin for treating rheumatoid arthritis.

Merck disputes the criticism of the Indocin research it sponsored. It says, among other things, that precise controls of the sort the committee demands are impossible in large-scale clinical testing and that physicians using the drug in their practices are finding it satisfactory. The company also notes that the Food and Drug Administration, which is responsible for policing the drug industry, cleared Indocin for marketing under its new rule requiring proof that the drug is effective as well as safe.

MOUNTING CONCERN

But it's unlikely that Merck will have an easy time quieting the criticism of the Indocin research. For the complaint comes as concern is mounting over the quality of medical research generally. Many doctors assert that sloppy research is leading to the employment of useless and even dangerous treatments in some instances.

The Food and Drug Administration, whatever its role in the Indocin controversy, has expressed sharp criticism of the work of some of the independent investigators who test new drugs for drug makers. "The hand of the amateur is evident too often for my comfort," says Dr. James Goddard, the FDA's chief.

Much of the uneasiness about medical research centers on drug evaluation. Drug companies allot millions of dollars in grants each year to medical schools and clinics whose staff members carry out evaluation studies.

But the caliber of research on new surgical or diagnostic techniques and other new medical procedures also is coming under fire. Freezing the stomach was publicized as a valuable new treatment for ulcers a while back, for example, but subsequent studies have convinced many physicians that it is practically useless.

THE FDA ACTS

The criticism of medical research is beginning to result in action. Some drug companies are tightening controls over investigations they sponsor. The Veterans Administration, which conducts extensive research at its facilities, is offering crash courses in research methods to personnel from its own hospitals and from affiliated medical schools. Also, the FDA is now trying to yank from the market several drugs on which research data has been questioned, and for the first time it is striking some physicians' names from the list of researchers allowed to test new drugs on human beings.

Despite the current concern, most doctors feel that medical research is better now than in the past. Dr. James Shannon, director of the National Institutes of Health, says scientists "are more precise and penetrating in their work now than in earlier years." Development of sophisticated new instruments and tests has enabled researchers to achieve greater precision, he says.

But critics assert that by today's standards research often isn't up to snuff. Dr. Goddard says he has been "shocked" by the poor quality of "many" of the proposed studies of new drugs submitted for FDA review.

UNANSWERED QUESTIONS

The NIH's chief or research on arthritis and rheumatism, Dr. John Decker, says that "perhaps half the studies proposed on the two diseases won't answer the questions posed because of inadequate design of the investigations." The faulty studies, which are proposed to the NIH for possible financing, are coming from "some of our better medical centers," Dr. Decker adds.

Stanley Schor, a professor of medical statistics at Temple University's medical school in Philadelphia, recently studied the quality of research reported in 10 of the top medical journals in the country. Included were the New England Journal of Medicine, the Archives of Surgery, the Annals of Internal Medicine, Surgery, Gynecology and Obstetrics, and the American Journal of Diseases in Children.

"In almost 73% of 149 reports critically evaluated," he stated, "conclusions were drawn when the justification for these conclusions were invalid."

Occasionally, Federal officials charge, sloppy research may be due to more than mere mistakes. Last year the FDA eliminated the names of Dr. Leo Cass and his associates in Cambridge, Mass., from its list of approved researchers. Dr. Cass operates three clinics. Among other things, the agency charged that some patients Dr. Cass claimed had received test drugs "were actually deceased." The FDA has turned the case over to the Justice Department for possible legal action. An attorney for Dr. Cass will say only that the physician still hopes to be reinstated as a researcher.

The FDA, however, already has initiated action to take three drugs off the market because evidence of the drugs' efficacy was based on Dr. Cass' allegedly faulty work. The drugs are Norgestic, a prescription pain-reliever made by a Rexall Drug & Chemical Co. subsidiary, and two sustained-release aspirin products—Abbott Laboratories' Stendin and Chesebrough-Pond Inc.'s Measurin.

"I'd like to have my hands on that investigator," exclaimed Dr. George Maison, a Rexall director, when he heard what Dr. Cass had allegedly done. But all three companies have vowed to fight the FDA moves against their drugs on grounds that other research supports the products.

Though there may be instances of intentional deception by researchers, the main source of concern is the conscientious investigator who slips up. It is such carelessness that can lead to bad medicine on a broad scale, critics say.

"DANGEROUS TECHNIQUES"

Temple's Mr. Schor says the errors he turned up in medical journals inevitably give rise to alarm over the possible effects of sloppy research on the practice of medicine. Dr. Harvey Dworken, a professor at Western Reserve University's medical school in Cleveland, says bluntly: "Shaky conclusions disseminated in lay and medical news media can lead to the rapid use of valueless or even dangerous techniques."

He cites the freezing treatment for ulcers as an example of a technique that he believes to be of questionable value.

On the basis of early research, the stomach-freezing technique was recommended for patients with duodenal ulcers. Freezing was said to halt the flow of acid in the stomach, thereby relieving pain and other symptoms of the ulcers. (The stomach was frozen by slipping a balloon down a patient's throat to the stomach, then inflating it with a cold liquid.)

The procedure was adopted by doctors before careful studies were made, Dr. Dworken charges. He adds that carefully controlled studies have now shown freezing is no better than conventional medical treatment and, in some cases, causes even more ulcers.

Dr. Owen Wangensteen, the University of Minnesota researcher who led development of stomach freezing, reported in a recent Journal of the American Medical Association that he has modified the technique and is beginning to achieve better results. He feels the modified technique may yet prove a useful tool against ulcers.

One common mistake by researchers is a failure to control experiments carefully. In a typical controlled test, one set of patients receives the new therapy while a control group—usually matched on the basis of age, sex and other factors—gets a placebo, or dummy therapy. The difference between the responses of the two groups indicates the value, if any, of the therapy on trial.

Inadequate control was one of the complaints made against Indocin by the arthritis specialists, whose report on the Merck product appears in the current issue of Clinical Pharmacology and Therapeutics. In rebuttal, Merck insists that its studies were as well controlled as possible consistent with the patients' well-being. It says some investigators were unwilling to treat patients solely with placebos for fear the arthritis would worsen during the test and become more resistant to treatment later on.

Controls were at issue in a dispute last year over Peritrate, a Warner-Lambert Pharmaceutical Co. drug. Peritrate had long been used to alleviate angina pectoris, a vise-like chest pain caused by heart disease, but the company mounted an ad campaign implying that the drug not only relieved symptoms but also prolonged life.

The Medical Letter, a publication that contains analyses of drugs written by a group of prominent physicians, questioned the experiment that was the basis for the new advertising approach. The Letter said several factors "suggest that more patients in the placebo (control) group than in the drug group were severely ill from the start." This would mean that more of those in the control group could naturally be expected to die and that Peritrate's implied power to prolong survival in the drug-taking group would be exaggerated.

AGE DIFFERENCES

The Letter also noted that the control group was older; 47 patients in it were 60 to 65, the age bracket in which most deaths in the study occurred. In the Peritrate group 33 were in that age bracket.

A Warner-Lambert official replied that "while there are differences in the groups, you would expect some because the patients were selected randomly. Statisticians tell us that the points at which our groups don't match don't negate the validity of the study."

But the FDA agreed with the Medical Letter. It seized a shipment of Peritrate, and Warner-Lambert called off its ad campaign.

Researchers testing new diagnostic tools face the danger of falling into the "false-positive" trap. A false-positive response to a diagnostic technique indicates a person has a disease when he really doesn't. A tool that regularly misleads a physician in this fashion is obviously worthless.

"Certainly, if checking for false-positives is not done, one can develop an excellent test for heart disease by counting a patient's ears," says Mr. Schor. "Everyone who has two ears has heart disease." Mr. Shor asserts blunders almost that incredible cropped up in some of the medical articles he reviewed.

Clumsy or superficial statistical analysis was another failing Mr. Schor says he frequently encountered in research reports. Of 149 medical articles scrutinized, says Mr. Schor, 51 had statistical defects.

A busy researcher's failure to exercise enough supervision over technicians also can lead to errors. According to the FDA, Dr. Albert Kligman, a prominent professor at the University of Pennsylvania's medical school, has in recent years supervised research on no less than 153 experimental drugs for 34 pharmaceutical companies. In 1966 the FDA changed that a Kligman-directed study on dimethyl sulfoxide (DMSO)—a chemical that has been tested against such varied afflictions as arthritis, bad bruises and a type of skin disease—contained numerous errors.

AN OVERLOOKED REACTION

In part of study, 20 men were supposed to have received the drug for 26 weeks. In fact some received it only 16 weeks and others dropped out of the study even earlier, the FDA charged. In addition, no severe reactions were reported by Dr. Kligman, but one patient actually developed giant hives on his skin, the agency said.

In an unusual letter to the Journal of the AMA, where his DMSO research had been published, Dr. Kligman conceded errors due to "inadequate supervision." The FDA struck his name from its list of researchers but reinstated him after he revamped his record-keeping procedures and promised to cut the number of drugs he will test and have future work monitored by another researcher, the agency said.

The episode was not the first blow for DMSO, a Crown Zellerbach Corp. commercial solvent that has tested for medical uses by no less than six companies—Merck, Syntex Corp., American Home Products Corp., Schering Corp., Geigy Chemical Co. and the Squibb subsidiary of Olin Mathieson Chemical Corp. Human testing was halted from late 1965 till a few months ago because of eye damage in test animals.

One reason conscientious researchers make mistakes is the great difficulty sometimes involved in the work. Arthritis, for example, is "an extremely variable disease; patients get better or worse for no apparent reason," says Dr. Becker of the NIH. As a result, it's tough for doctors to determine whether a new drug is really helping patients get better or whether they would get better anyway, he says.

OBJECTIVE TESTS

On the other hand, the physicians who criticize the Merck-sponsored research on the use of Indocin to treat arthritis say some participating investgators failed to employ objective tests that were available to assess a patient's condition, relying instead on subjective judgments. The objective criteria include walking speed, strength of grip, a blood analysis and measurements of finger joint swelling made with rings in graduated sizes.

Some authorities say faulty investigations result to a considerable extent from the scarcity of formal training for researchers. Dr. Harold Schoolman, a researcher at the VA hospital in Hines, Ill., calls medical research "a profession peopled by amateurs."

"There is no mystery" why an investigator falls short in statistics, a recent AMA Journal editorial states. "The meager bio-statistical fare offered by the medical curriculum does not prepare him for the stringencies of statistical analysis. Nor is his contact with statisticians during postgraduate years close enough to permit frequent consultations."

To protect themselves, some drug companies are increasing their control over research they support. Upjohn Co., for example, is tending to exercise more control over the design of experiments, an Upjohn official says. In the past, independent investigators working on Upjohn-sponsored projects have been left largely free to draw up their own research plans.

[Clinical Notes]

[From Journal of the American Medical Association, Mar. 20, 1967, vol. 199, No. 12]

SUDDEN DEATH IN ARTHRITIC CHILDREN RECEIVING LARGE DOSES OF INDOMETHACIN*

(By Jerry C. Jacobs, M.D.)

Death in children with rheumatoid arthritis is rare. A review of 110 cases seen at the Columbia-Presbyterian Medical Center from 1928 through 1956 reported eight deaths.[1] From 1952 to 1963, 79 new juvenile patients with rheumatoid arthritis were seen. Although corticosteroids were used in many children during these years, none died. Of the eight deaths occurring in the preceding 36 years, one was from hepatitis following therapeutic blood transfusions commonly administered in earlier years, two were from secondary amyloidosis, one from diabetic acidosis, one from acute appendicitis, one from colitis, and one occurred during induction of anesthesia one day after therapy with prednisone was discontinued. At the time of death, five of these eight patients were adults with long-standing rheumatism (11 to 22 years); only three died during childhood. None had overwhelming infection. In the past three years, however, two arthritic children seen in our hospital have suddenly become acutely ill and died within 72 hours. Both children were in other hospitals at the time of death and physicians in attendance hours before death did not anticipate their demise.

REPORT OF CASES

CASE 1.—This 6½-year-old boy first developed swollen ankles and low-grade fever in 1959 at the age of 2. After two months of therapy with aspirin, he improved and did well until 1961 when at the age of 4½ he again developed polyarthritis, fever, and a rash typical of juvenile rheumatoid arthritis. He was treated with prednisone, 20 mg daily, and aspirin, 2.4 gm daily. Repeated attempts to reduce the prednisone dose below 10 mg daily were unsuccessful even with the addition of indomethacin, 180 mg daily (9 mg/kg of body weight), in May 1962. At that time, this drug was under clinical investigation and the recommended dose for adults had not been established. No symptoms of a toxic condition in this patient were reported. During the summer, x-ray films of the hips disclosed aseptic necrosis of the right femoral head. When he was admitted to the Babies Hospital in October, it was possible to reduce the prednisone dose to 5 mg daily. After discharge, the dose was gradually reduced further to an average of 1.5 mg daily. Treatment with aspirin and indomethacin was continued.

On Jan 6, 1963, he was seen by his pediatrician, thought to have mild bronchitis and laryngitis, and was treated with sulfisoxazole and an expectorant, dexchlorpheniramine maleate. On Jan 22 his temperature rose to 105 F (40.6 C) and minimal signs of upper-respiratory tract infection were noted. No treatment was given. On the following day, there was diarrhea and vomiting which subsided without treatment. When next examined on Jan 24, he was afebrile, drowsy, and had erythematous blotches on his feet. He was admitted to his community hospital and treated with intravenous fluids. He seemed to improve but became stuporous, developed labored respirations, and died 3½ hours after admission. He had received his regular daily dose of prednisone on the day of death.

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*From the Department of Pediatrics, Columbia University College of Physicians and Surgeons, Babies Hospital, and Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York.

Reprint requests to 3975 Broadway, New York 10032.

[1] Grokoest, A. W.; Snyder, A. I.; and Schlaeger, R.: *Juvenile Rheumatoid Arthritis*, Boston: Little, Brown & Co., 1962.

Postmortem examination performed ten hours later revealed serofibrinous pericardial adhesions, a 1½-cm gastric ulcer without evidence of bleeding, yellowish turbid fluid in the ileum and jejenum without evidence of inflammation, and absence of feces in the large intestine. A blood culture was not obtained. All lymphoid tissues showed evidence of acute and chronic involution with marked reticulosis. On some lymph nodes and in the spleen, the reticulum cells in the center of follicles formed epithelioid aggregates. (Fig. 1) A normal number of plasma cells was found in the intestine and adequate numbers of neutrophils were seen in the blood vessels of all tissues. Dense neutrophilic infiltration was present in portal triads. The cause of death remains obscure.

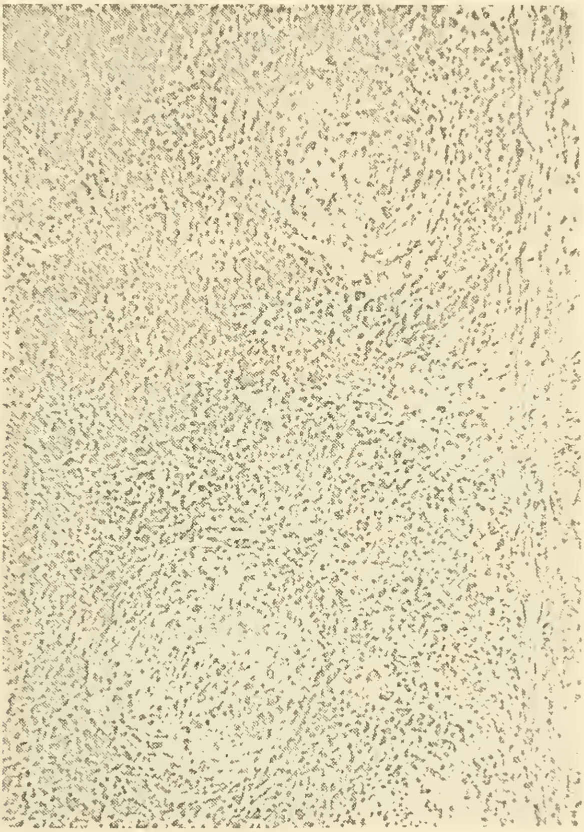

FIGURE 1.—Lymph node (case 1). Cortical areas showing marked reticulosis and epithelial aggregates in center of follicles (medium magnification).

CASE 2.—This 9½-year-old girl developed monarticular arthritis of the right knee at age 2 years and 9 months which became generalized polyarthritis in May 1960 when she was 3½ years old. When first seen in this institution in September, physical examination revealed slight limitation of extension of the left wrist and a five-degree flexion contracture of the right knee but movement was otherwise within normal limits. Although she was treated with aspirin, her disease progressed and in November prednisone, 4 mg daily, was instituted. Prednisone was given in doses of 1 to 4 mg daily until August 1963 when it was discontinued. The disease was continuously present with varying degrees of activity and some progressive limitation of motion in all her joints.

On Feb. 12, 1965, indomethacin therapy, 25 mg three times daily, was begun; aspirin, 1.5 gm daily, was continued. On March 26, the dose of indomethacin was increased to 100 mg daily (4 mg/kg body weight) and there seemed to be some improvement. By July the child was so well that the parents abruptly stopped giving the indomethacin. The arthritis exacerbated one month later, and in August, treatment with indomethacin, 75 mg daily, was reinstituted. When no improvement was observed, the drug was again discontinued in October. The patient's conditions became much worse and the same month treatment with indomethacin, 75 to 100 mg daily, was again reinstituted and the dose of aspirin was increased to 2.4 gm daily. She did not improve and in February 1966 was admitted to a convalescent hospital for more vigorous physiotherapy.

On April 16, she became febrile. On April 17, she was examined by a consulting pediatrician who fund a tender swelling over the right parotid gland and thought she had mumps. Several hours later her skin was noted to be mottled. During the following five hours, her condition rapidly deteriorated and she died. Postmortem examination on the following day revealed evidence of acute sepsis in many organs (Fig. 2 and 3). There was extreme bilateral adrenal congestion. Fibrin thrombi, which were found in some renal and pulmonary arterioles and in adrenal cortex capillaries, contained bacterial colonies. The portal triads were infiltrated with neutrophils. Except for evidence of acute stress reaction, lymphocytes and plasma cells were present in adequate numbers. A culture of cisternal fluid mixed with blood obtained post mortem grew group A β-hemolytic streptococci. It was concluded that she had died of overwhelming sepsis.

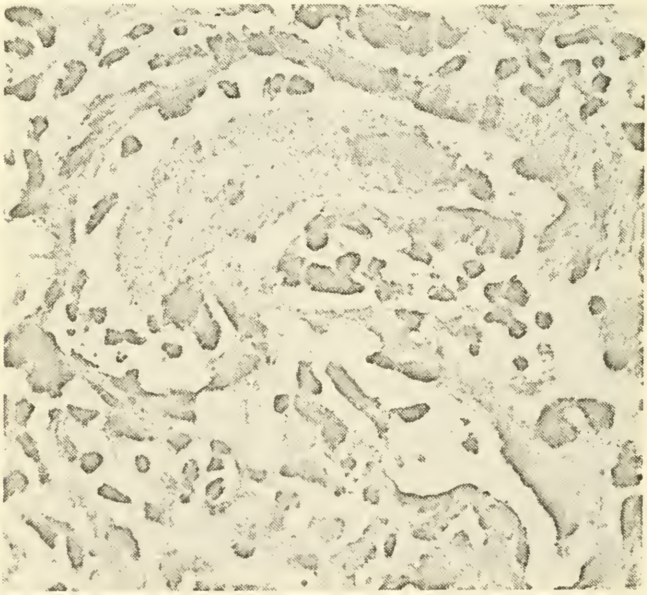

FIGURE 2.—Kidney (case 2). Fibrin thrombus with bacterial colonies in afferent arteriole of glomerulus (high magnification).

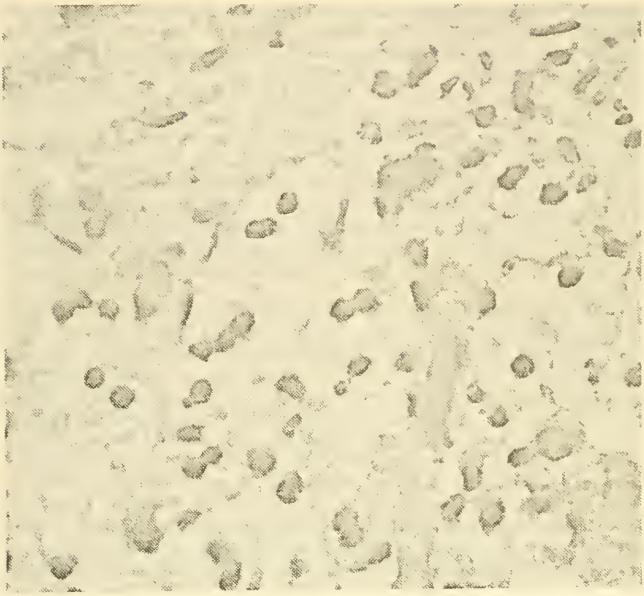

FIGURE 3.—Adrenal cortex (case 2). Bacterial colonies in capillaries (high magnification).

COMMENT

Indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, is a recently developed nonsteroid, antiinflammatory agent found useful in some cases of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and gout. In early studies on adult patients, gastrointestinal hemorrhage and perforated peptic ulcer were infrequent serious complications: milder side effects included headache, faintness, giddiness, nausea, and diarrhea. While large numbers of adults were studied in reliable clinics, young children were not included in the original tests and a dosage schedule for children has not been established. The manufacturer has not recommended its use in children.[2]

Adults generally receive between 50 and 200 mg of the agent daily: larger doses produce adverse side effects and are not recommended. The children reported herein weighed btween 20 kg (44 lb) and 25 kg (56 lb) but received doses which might be used in adults (100 to 180 mg daily). Both patients took the drug for more than a year without observed ill effects and both appeared to achieve some relief of their arthritis.

The influence of indomethacin on resistance to infection has been studied by the manufacturer.[3] In mice and rats, usual anti-inflammatory doses did not affect resistance, while with larger doses there was some evidence of *enhanced* resistance. However, in rabbits, repeated large doses decreased resistance to pneumococcal infection which was produced by injecting virulent pneumococci into the skin of the animals. (This effect was not demonstrable with lower doses.) In another experiment with doses of 10 mg/kg/day, the spontaneous mortality of rabbits was high. When killed after ten weeks of treatment, they had a significantly increased incidence of subcutaneous abscesses, pneumonia, and pericarditis of infectious origin. Enhancement of spontaneous infection has also been demonstrated experimentally in the guinea pig and dog but not in the monkey.

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[2] *Informational Product Circular*, West Point, Pa.: Merck, Sharp & Dohme, July 1, 1965.

[3] *Informational Material on Indocin*, West Point, Pa.: Merck, Sharp & Dohme Research Laboratories, June 15, 1964.

Reports of increased susceptibility to infection in subjects receiving indomethacin have not been convincing. There are a few reasonably well documented cases of leukopenia associated with indomethacin therapy. A recent report from South Africa[4] suggests the possibility of activation of latent infection by indomethacin. However, in the three patients reported in the South African study signs of septic arthritis developed within two weeks of initiation of indomethacin therapy and a relationship between the administration of the drug and the septic processes is uncertain. To date, there is little or no evidence that customary doses used in adults with beneficial effects result in increased susceptibility to infection.

However, both our experience and the experimental data cited suggest that unusually high doses may have such effects. While thousands of adults have received indomethacin, the number of children known to have been under prolonged treatment with this drug is small. Two of seven children receiving the agent in the arthirtis clinic died. This observation is of enhanced significance when compared with our experience of only three known deaths among juvenile patients with arthritis in the preceding 35 years. With extensive use of steroids in our clinic during the years 1953 through 1963, no children died.

Death has been uncommon in other reported series of juveniles with arthritis (about 6% in children followed over a long period in general hospitals). However, infection has been a more important cause of death in other series than in our own, accounting for 25% of the deaths in one clinic and occasionally occurring in children not treated with steroids.[5] (This is not surprising since infection is the third most common cause of death in children, and accounts for about 17% of all deaths between the age of 1 and 14 years.[6] Death from adrenal failure may occur in children who have received steroids in the preceding year unless additional steroids are administered during subsequent acute illness or surgery.

While the evidence is circumstantial and we cannot be certain that there is any relationship between the drug indomethacin and either the unexpected death of these patients or increased susceptibility to infection, this clinical experience and the existing experimental data indicate that such relationships may exist. Under these circumstances, it would seem appropriate to restrict the use of the drug in children to those in whom other agents do not provide satisfactory results and to be alert to the possibility of overwhelming infection. Sudden onset of high fever may be the only indication of a life-threatening illness.

SUMMARY

Acute febrile illnesses developed in two children with rheumatoid arthritis, who were followed at the Columbia-Presbyterian Medical Center, New York and death occurred within 72 hours. These were the only deaths in this group of children during the past 14 years. Both children were receiving indomethacin as part of their therapeutic regimen. Physical examination shortly before death did not suggest the impending danger. In one patient, post-mortem examination showed no definite cause of death. Group A β-hemolytic streptococcal septicemia appeared to be the immediate cause of death in the other. No comparable experiences have been reported in adults. Until further information is available, it would seem reasonable to use indomethacin only in children not responsive to other agents, to limit the dose, and to be alert to the possibility of overwhelming infection.

Following preparation of this report, two additional cases of unexpected death in arthritic children have been reported by the Merck Sharp and Dohme Company. One was that of an 8-year-old girl who received indomethacin, 50 mg daily for one month. She was discharged from her community hospital 48 hours prior to her unexpected death. At home she suddenly became acidotic, comatose, and icteric. She was readmitted to the hospital but died in eight hours. Autopsy revealed large zones of hepatic necrosis with heavy periportal inflammatory cell in-

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[4] Solomon, L.: Activation of Latent Infection by Indomethacin: A Report of Three Cases, *Brit. Med. J.* 1: 961–962 (April 16) 1966.

[5] Ansell, B. M., and Bywaters, E. G. L.: Rheumatoid Arthritis (Still's Disease), *Pediat. Clin. N. America* 10: 921–939 (November) 1962.

[6] *Summary of Vital Statistics, 1964,* Department of Health, the City of New York.

filtrates, some membranous glomerulitis and tubular necrosis in the kidneys, and findings of juvenile rheumatoid arthritis. Cultures of the blood showed no growth. The administration of prednisone had been discontinued one month previously. The other patient was an 11-year-old boy who developed jaundice and severe gastrointestinal bleeding after receiving indomethacin, 100 mg daily for two months. He also was receiving an unknown dose of prednisone. Cultures of the blood showed no growth. Despite therapeutic efforts, he died within two weeks. Autopsy showed hepatic necrosis, ascites, and juvenile rheumatoid arthritis.

Drs. Leroy Engel and William C. Ivins, Jr., provided clinical data and gave permission to include their patients in this report. Drs. Victoria A. Bradess and Campbell A. McNicol performed the autopsies. The Medical Examiner's Office of Suffolk County provided the pathologic data in case 1. Dr. William A. Blanc reviewed the microscopic pathologic material.

Generic and Trade Names of Drugs

Prednisone—*Deltasone, Deltra, Meticorten, Paracort, Cotone, Lisacort, Metasone.*
Indomethacin—*Indocin.*
Sulfisoxazole—*Gantrisin, Sulfoxol.*
Dexchlorpheniramine maleate—*Polaramine Maleate.*

[From Medical Tribune, Mar. 29, 1967]

FDA STATEMENT CITES ACTION ON INDOCIN

WASHINGTON, D.C.—The Food and Drug Administration issued the following statement on Indocin:

"The Food and Drug Administration maintains surveillance over the safety and efficacy of any new drug. In the case of Indocin, which was approved for marketing on June 10, 1965, this surveillance has already resulted in changes in the drug's labeling. These revisions involved stringent warnings emphasizing that the drug should not be used in children. The revised labeling was distributed to physicians by first-class mail last December. In addition, the advertising program for the drug was modified drastically to a more conservative approach.

"When surveillance of a new drug produces new evidence in the form of reports of lack of efficacy, this information is reviewed together with previously available data to reevaluate the claims made for the drug.

"When such additional information makes changes necessary, the indications for use of the drug may be modified or other appropriate measures taken."

[From Medical Tribune, Mar. 29, 1967]

MERCK CRITICIZES DESIGN OF STUDY AS NOT VALID

RAHWAY, N.J.—Merck & Co., Inc., has issued the following statement in comment on the cooperative study of indomethacin:

A study sponsored by the American Rheumatism Association, under a grant from the National Institutes of Health, appeared in the January-February issue of *Clinical Pharmacology and Therapeutics*, with Dr. Donald Mainland as the principal author. It is primarily a biostatistical attempt to establish objective criteria for the evaluation of therapeutic agents used in the management of rheumatoid arthritis.

In the Mainland study, patients were divided into two groups. One group received indomethacin and the other received placebo; however, patients in both groups were permitted to take as much aspirin as desired. Then several tests—morning stiffness, grip strength, walking time, erythrocyte sedimentation rate, and numbers of clinically active joints—were used to attempt to ascertain whether there were any objectively measurable differences between these two drug regimens. It turned out that the investigators were able to observe no significant differences. The study was not designed in any sense to show, and does not show, the clinical effectiveness of indomethacin used alone or the relative effectiveness of indomethacin and aspirin used separately.

Aspirin can be used successfully in the management of some cases of rheumatoid arthritis. Indomethacin is one of the drugs prescribed for patients whose rheumatoid arthritis cannot be successfully managed by aspirin. Aspirin, though an extremely useful drug, has also been highly unsatisfactory in the management of osteoarthritis of the hip, ankylosing spondylitis, and acute episodes of gout—all of which have been successfully managed with indomethacin. Thus, there cannot be a valid comparison of the relative therapeutic value of the two drugs for all of their indications, and the Mainland study is not a valid comparison of the two drugs even as to the indication they have in common.

The study demonstrates fully that it is difficult to establish and successfully apply objective criteria that would permit measurement of the relative value of various drugs used in the management of rheumatoid arthritis. Scientists at Merck have good reason to remember that this is not a new problem. At the time of cortisone introduction—and Merck research had a key role in that development—several distinguished independent clinical investigators undertook to establish the value of steroids in the treatment and the management of rheumatoid arthritis by utilizing objective measurements. They were unable to do so. Similar efforts to establish objective measurements of the values of aspirin in managing this condition have also failed. Yet no one would maintain, because of the lack of success in these efforts, that either cortisone or aspirin is ineffective in the management of rheumatoid arthritis.

We are puzzled about the comment by Dr. Mainland and his coauthors on the quality of much of the previous research on indomethacin, as reflected in the literature available to them, and about the point they are trying to make with regard to the use of controls. Even in their own study, there were no nondrug placebo controls in the usual sense, since all of the patients were permitted to receive as much aspirin as they desired or needed to control the disease throughout the study.

While it would be theoretically desirable in controlled studies in rheumatoid arthritis to utilize placebo control patients, double-blind techniques, and objective methods of measurement, a complication is the investigator's unwillingness, even inability, to compromise at any time the physical well-being of the test patient. The conduct of long-term double-blind studies in rheumatoid arthritis patients has been, in the experience of many investigators, extremely difficult because most patients with active rheumatoid arthritis consume aspirin or some related analgesic as a daily routine without regard to their physicians' directions.

PERILS OF PLACEBO USE

In addition, denying effective therapy to arthritic patients, which is the only way to use them as placebo controls, places them in danger of regressing to such a degree that previous levels of management are no longer attainable.

The evidence establishing the safety and therapeutic effectiveness of Indomethacin that was submitted to the FDA by the Merck Sharp & Dohme Research Laboratories included studies by more than 300 clinical investigators. Many of the studies were on rheumatoid arthritis, and among these were controlled studies utilizing placebo, studies alternating indomethacin and placebo using patients as their own controls, and several double-blind studies. Some have been published in the medical literature, and others though unpublished are contained in the New Drug Application and served as part of the evidence on which the FDA approved the claim for the effectiveness of the drug in rheumatoid arthritis.

The clinical investigations that have been carried out around the world with indomethacin, the continuing clinical studies, and the wealth of successful physician and patient experience with the drug demonstrate its effectiveness for those conditions for which it is approved.

[From Medical Tribune, Mar. 29, 1967]

RESULTS OF 11-CENTER ARTHRITIS DRUG STUDY—INDOMETHACIN, PLACEBO FOUND "INDISTINGUISHABLE"

NEW YORK.—Indomethacin, which has recently been a focal point of attention because of reported side effects and toxicity, as well as its advertising claims (MEDICAL TRIBUNE, December 7, 1966), has now been declared to be virtually indistinguishable from a placebo in an 11-center study of rheumatoid arthritis patients.

The recently developed compound, widely used as an anti-inflammatory and analgesic agent in arthritic disorders, showed no "real differences" from placebo as judged "by the over-all impression of physicians or patients, or by the combination of all objective and subjective measures by an optimal weighting technique," the study declared.

This was the finding reported by the Cooperating Clinics Committee of the American Rheumatism Association after a three-month blindfold trial of 136 patients with peripheral rheumatoid arthritis.

Dr. John L. Decker, chief of the arthritis and rheumatism branch of the National Institute of Arthritis and Metabolic Diseases, who participated in the study, told MEDICAL TRIBUNE that on the basis of this and other studies, "it seems likely that, in the last analysis, indomethacin may prove to be a not very good drug."

The A.R.A. study, prepared by Dr. Donald Mainland, Professor of Medical Statistics at New York University, is the product of approximately 18 months of planning and analysis, and was designed to overcome what were felt to be deficiencies in earlier trials of indomethacin in rheumatoid arthritis, Dr. Mainland told MEDICAL TRIBUNE. It is the latest in a series of investigations that are challenging the claims for indomethacin as a specific of unusual promise in rheumatoid arthritis.

A recent Boston study by Drs. Robert S. Pinals and Sumner Frank reported that it was difficult to detect differences between indomethacin and aspirin in a three-month double-blind trial of 24 patients with rheumatoid arthritis.

In commenting on the study, Dr. Pinals told MEDICAL TRIBUNE that "the most important single finding that is beginning to emerge from investigations like ours is that indomethacin is not significantly better, if at all, than aspirin or placebo."

He was referring not only to his own trial but also, as cases in point, to two recent British studies that suggested that differences between indomethacin and placebo and between indomethacin and aspirin were virtually undetectable in double-blind crossover trials of rheumatoid arthritis patients.

Discussing one of these, Dr. Kenneth Lloyd, director of the department of physical medicine and rheumatology at United Cardiff Hospital, Wales, described the findings in a 10-week double-blind crossover study of indomethacin and a placebo in 28 patients. The investigation, he told MEDICAL TRIBUNE, failed to show that the drug produced any analgesic or detumescent effect. Further using a variety of objective criteria for assessing symptom changes "it was not possible to show that indomethacin produced any antiphlogistic effect that held statistical validity."

"I never thought that indomethacin had any promise in rheumatoid arthritis, and my impressions were confirmed by our trial," he commented.

A similar view was expressed by Dr. Ronald Harris, director of rehabilitation at Devonshire Royal Hospital, Buxton, and coauthor of a four-week crossover trial of indomethacin and soluble aspirin in 38 patients with definite and classical rheumatoid arthritis. The patients were a uniform group, "all in the same category of disease," he told MEDICAL TRIBUNE. The trial failed to disclose statistically significant difference between indomethacin and aspirin, he said.

"The initial claims for indomethacin in the treatment of rheumatoid arthritis," he observed, "may have been premature."

These reassessments of the drug, investigators have pointed out, stem from two factors. The first is the attrition of early claims that may often occur as clinical experience accumulates in the use of a new compound. Indomethacin has been available to the practitioner since June, 1963, and patient-days of therapy are in excess of 144,000,000, according to the manufacturer, Merck Sharp & Dohme.

EARLY CLAIMS QUESTIONED

The second reason for the fresh and harder look at indomethacin, however, is the growing belief among some investigators that the early claims for the drug were unduly optimistic because they were based on inadequately designed and/or improperly evaluated trials. This was an important consideration behind the trial set up by the American Rheumatism Association.

"One of our primary reasons for undertaking our multicenter study of indomethacin," said Dr. Mainland, "is that we were dissatisfied with the quality of much of the research initially done on the drug. These reports led to more promising conclusions than . . . evidence warranted."

Dr. Mainland, who is a member of New York University's Study Group on Rheumatic Diseases, said that the Cooperating Clinics Committee sought to design a trial that would avoid "the pitfalls in inferences" that had chareterized some earlier indomethacin studies in rheumatoid arthritis, and that would be "as close as we could get to actual clinical practice."

Like others critical of the earlier findings, he stressed that Merck Sharpe & Dohme had never sought to affect an investigator's conclusions.

The cooperating institutions in the study included Southwestern Medical School; State University of New York, Downstate Medical Center, Brooklyn; University of Illinois; University of Chicago; University of California and Veterans Administration Hospital, Los Angeles; Massachusetts General Hospital, Boston; Jackson Memorial Hospital, Miami, Fla.; Rackham Arthritis Research Unit, University of Michigan; Presbyterian Hospital, New York; University of California, San Francisco; University of Tennessee; and University of Washington, Seattle.

STUDY CITES 46 REPORTS

The A.R.A. study cites 46 reports that have appeared on the use of indomethacin in rheumatoid arthritis since 1963, and comments: "In general the degree of enthusiasm for the drug varied inversely with the quality of the investigation. For example, in those reports that contained no objective measures of joint function, 56 percent of 607 cases of rheumatoid arthritis were stated to have improved when treated by the drug, whereas in those reports that contained evidence of objective measures, only 34 per cent of 218 cases were classified as improved."

In the A.R.A. cooperative trial, the investigators conducted a blindfold study of arthritic symptom changes and the frequency of nonarthritic symptoms in 71 indomethacin-treated and 65 placebo-treated adult patients with peripheral rheumatoid arthritis. Both groups of patients were permitted to continue on salicylates, since salicylates are "commonly permitted in conjunction with other anti-rheumatims therapy," the committee pointed out. Excluded from the trials were patients who had received indomethacin at any time, or steroids, antimalarials, or gold therapy within a recent period. Twenty-seven patients withdrew from the trial before it ended, leaving a total of 109 for the full study.

The patients ranged in age from 16 to 81 years, with a median between 52 and 53. The duration of disease ranged from six months to 36 years, with the median between five and six years. "The two treatment groups did not differ appreciably in the distribution of age or disease duration," the report noted.

Five relatively objective measures of results were employed; numbers of clinically active joints, grip strength, morning stiffness, erythrocyte sedimentation rate, and walking time, as well as phyicians' and patients' impressions.

The daily doses of indomethacin, in capsules, were increased from 50 to 200 mg. over the period of study.

In summarizing their findings, the investigators stated: "The drug and placebo groups were indistinguishable in frequency, extent, and rate of change of symptoms, evaluated either singly or in combination. Undesirable symptoms, especially headache, dizziness, and lightheadedness were more frequent in the drug group than in the placebo group.

One week after trail medication had ceased, and before treatment assignments had been fulfilled," the report said, "physicians' and patients' impressions recorded a much higher frequency of deterioration in the drug than in the placebo group. The average duration of morning stiffness reflected the same difference."

In commenting on the results, the study made this point: "Comparison of the two treatment groups in this trial showed no justification for choosing indomethacin with aspirin in preference to placebo with aspirin. None of the recorded pretrial characteristics of the patients indicated which of them would be most likely to benefit from the drug. There was an excess of undesirable nonarthritic symptoms in the drug-treated patients, but their frequency was rendered somewhat less impressive by the occurrence of the same symptoms in some placebo patients."

The committee stated that one of the "pitfalls" in drug trials is that investigators fail to recognize "the subordinate and limited role of statistical 'significance' tests." The report noted that, in setting up the cooperative trial, some physicians had urged that efforts be made to demonstrate "significant differences" between the drug and placebo, "to disprove a null hypothesis." A null hypothesis is one that predicts there are no differences between two agents. In turning down these proposals, the committee said that it was not questioning "the possibility that indomethacin benefits some patients."

But it went on to say, "Even if the proposed techniques produced numerous 'significant' differences (although the data show little likelihood of this), these verdicts would not alter the observed small degree of benefit attributable to the drug under the conditions described."

The study was published in the January–February issue of *Clinical Pharmacology and Therapeutics*.

Dr. Louis C. Lasagna, of Johns Hopkins University, who served as consultant to the committee, told MEDICAL TRIBUNE that the findings tended to confirm his own early impressions "that what we had in indomethacin was another aspirin-like compound."

"I never thought of indomethacin as a breakthrough," he said. "It seemed to me that it was just another drug to add to our armamentarium in rheumatoid arthritis."

SIGNIFICANCE SPELLED OUT

Dr. Lasagna, who is Associate Professor of Medicine and Associate Professor of Pharmacology and Experimental Therapeutics, said: "It changes our perspective if indomethacin is not a breakthrough but only another aspirin-like compound. This means it may be useful in some cases where aspirin is not. But this study ought to dampen the enthusiasm of those physicians who look upon indomethacin as a super-drug."

The 11-center study by the American Rheumatism Association injects yet another dispute into discussions of a drug that has been the focus of controversy, both in the United States and Canada, over the past year. A later article will detail the drug's problems with both the U.S. Food and Drug Administration and the Canadian Food and Drug Directorate as accumulating clinical experience pointed to serious toxic effects and to fatalities associated with the use of the drug.

But the view emerging in some recent studies of this widely used and popular compound may have been summed up by Dr. Decker: "On the basis of the evidence coming in from more careful studies, it seems likely that in the last analysis, indomethacin may prove to be a not very good drug."

Stressing that Merck Sharp & Dohme is a "most reputable firm," he added: "It may be true to say that indomethacin has turned out to be a disappointment. Admittedly, it would be difficult to get investigators to do the exacting kind of work required to evaluate this kind of agent in early trials. Perhaps the first five trials of a drug of this type should be carried out with exquisite exactitude, instead of having 50 less than adequate studies that require several years of re-evaluation."

[From Medical Tribune, Apr. 3, 1967]

ACTIVE HISTORY OF REASSESSMENT FOR ANTIARTHRITIS DRUG—INDOMETHACIN EFFECTS RECEIVE WIDE SCRUTINY

NEW YORK.—Although the studies that are challenging indomethacin's efficacy in rheumatoid arthritis are of recent date (MEDICAL TRIBUNE, MARCH 29), the drug's reported toxicity and side effects had already brought it under governmental scrutiny in the United States and Canada last spring.

Deaths in children who had been receiving indomethacin, a higher than expected incidence of central nervous system reactions, and reports of blood dyscrasias and agranulocytosis had alerted regulatory agencies in both Washington and Ottawa.

Other reports had noted that indomethacin apparently masked the signs and symptoms of an infectious process and may even have activated latent bacterial infections.

Such findings in a drug that had risen, in a words of a top Food and Drug Administration official, to the ranks of the "Big Eight" among medicine's newest compounds, were bound to evoke the closest attention among the authorities.

DRUG PRESCRIBED FREQUENTLY

The most frequent prescription written today for a nonsteroid antiarthritic drug other than aspirin names indomethacin. The drug's wide acceptance in clinical use thus called for particular care in assessing its safety as well as its efficacy. At the same time, the rapidly developing clinical experience with indomethacin made it possible for investigators to evaluate its claims earlier than usual.

When indomethacin was introduced by Merck & Co., Inc., in June, 1965, after extensive experimental and clinical trials, the drug seemed to fill an important gap in the medical armamentarium. It was described as a new "antirheumatic," nonsteroid compound of value in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, and gout. These claims, and their very wording, were authorized by the FDA.

The original literature noted that "unlike corticosteroids, Indocin (indomethacin) has no effect on pituitary or adrenal function. It is well-suited for long-term as well as short-term use in adult patients of all ages." The package insert stated that, in the conditions for which it was indicated, indomethacin "may often replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds and colchicine."

Among the earlier reassessments of the drug was a South African study reported last April by Dr. L. Solomon, of the Rheumatism and Arthritis Unit in Johannesburg General Hospital. Challenging the view that indomethacin, does not diminish resistance to infection, he reported three cases in which latent infection had been activated in patients undergoing indomethacin therapy. In one, a covert infection of the hip was brought to light; and in the other two a known or suspected septic arthritis contracted earlier was reactivated after administration of indomethacin. Dr. Solomon declared in the study, published in the *British Medical Journal.*

FOURTH CASE ENCOUNTERED

He told Medical Tribune [Medical Tribune, June 6] that a fourth case had been encountered, after the study was published—that of a 45-year-old woman who developed full-blown septic arthritis of the knee during indomethacin therapy. She recovered after treatment with antibiotics.

Dr. Solomon suggested that since indomethacin does not cause a reduction in antibody formation or phagocytic activity, the activation of latent infection might have stemmed from a breakdown of local barriers to the spread of infection.

In reply, Merck & Co., Inc., told Medical Tribune [Medical Tribune, June 6] that the South African study covered only three or four cases and "provides no basis for ruling out coincidence."

Reports of adverse reactions continued to accumulate as clinical experience mounted. By last fall, both the Food and Drug Administration and the Canadian Food and Drug Directorate had received reports of more than 300 adverse reactions, including seven deaths in children and nine in elderly persons.

The FDA called the relation clear-cut in one fatality, possibly clear-cut in three others, and highly questionable in the rest. The Canadian agency, noting that "several deaths" had been reported in children with severe forms of rheumatoid arthritis and rheumatic fever who had been getting indomethacin, declared: "The exact relationship to indomethacin was difficult to develop in these reports. However, we recommend that indomethacin should not be used in children until the results of further studies become available."

A Merck spokesman, in commenting on the fatalities in children, noted that all were "suffering from Still's disease or severe juvenile rheumatoid arthritis and were receiving other drug therapy in addition to Indocin. The advanced stages of this severe collagen disease are usually characterized by critical involvement of the blood, pericardium, liver, spleen, and lymph nodes. After other drugs had failed, physicians weighing the possible risks of therapy with a promising new medication against the consequences of an untreated degenerative disease administered Indocin in an attempt to alter the course of the disease."

The American and Canadian agencies diverged in their response to the growing reports of adverse reactions. Following discussions between Merck representatives and FDA authorities, the company revised the package insert and sent an advisory letter to all physicians. Stamped "Drug Safety Information," the letter called attention to the changed insert and noted that revisions were being printed in boldface, for easy recognition.

Among the major changes were deletion of the description of indomethacin as an "antirheumatic" drug; deletion of the phrase "of all ages" in describing adults in whom the drug may be used; addition of the statement that indomethacin is effective in "symptomatic" treatment of the disorders for which it is indicated. The revised package insert stressed that the "drug should not be prescribed for children because safe conditions for use have not been established." It noted that "in a few cases of severe juvenile rheumatoid arthritis who were receiving Indocin along with other drugs, severe reactions, including fatalities, have been reported."

CANADIAN UNIT ACTED DIRECTLY

In Ottawa, however, the Food and Drug Directorate acted directly to warn the medical profession of the newly reported adverse reactions. In a "Dear Doctor" letter to Canadian physicians, R. A. Chapman, Ph.D., director-general of the FDD, noted that the agency had received reports of adverse reactions, "the severity or nature of which were unknown at the time the drug was released."

Citing some of the problems encountered in clinical use of the drug, the letter declared: "It is now apparent that indomethacin can mask the signs and symptoms of an infectious process or activate a latent bacterial infection. These complications are similar to those observed with corticosteroids and other anti-inflammatory drugs."

The warning added: "The possibility of a concurrent infectious process in your patients receiving indomethacin should be constantly borne in mind. If symptoms and signs suggestive of infection appear, discontinuation of the drug should be considered and vigorous therapy initiated."

Commenting on the deaths in children, the letter noted: "Some of these children succumbed to an intercurrent infection, the severity of which may have gone unrecognized during treatment. The exact relationship to indomethacin was difficult to determine in these reports." Like its U.S. counterpart, the FDD advised physicians not to use the drug in youngsters.

LETTER MENTIONS REVISIONS

The letter added that the manufacturer was revising the package insert to include "information on all these reactions," but that the FDD was notifying physicians in advance and requesting reports of any actual or suspected adverse reactions in patients using indomethacin.

Dr. Geoffrey Bishop, chief of the FDD Division of Medicine and Pharmacology, said that, in warning physicians about the reported fatalities, "Our intention was not to say dogmatically that the deaths were due to indomethacin, but to communicate our suspicions to the medical profession. That's the essence of the reporting program," he added. "You get suspicious. We also received reports of blood dyscrasias and of agranulocytosis. We began to get suspicious also that agranulocytosis might be due to the drug."

The disparity in response between the American and Canadian agencies to what were essentially the same clinical data prompted queries in both Washington and Ottawa. Dr. Herbert Ley, Jr., director of the FDA Bureau of Medicine, told MEDICAL TRIBUNE that the differences between the Canadian warning letter and the "Drug Safety" advisory issued in the U.S. by Merck was one of degree. He said that the FDA did not feel a warning letter of the Canadian type was justified since, "to the best of our ability, we have been able to find no major change in toxicity of this drug." Primarily, he said, the FDA was concerned not with "a sudden development of unsuspected toxicity but with an improper emphasis on the drug's usage in the company's advertising campaign."

Laying stress, in his discussion, on the advertising of indomethacin, he said that the company had been making "open-ended advertising claims" that did not sufficiently delimit the uses of the compound. For example, he declared, indomethacin was originally described as an "antirheumatic" agent. "Now a rheumatologists would know what that means," Dr. Ley said, "but a physician in general practice, particularly an older man, might find it misleading. It would appear from the Canadian letter that some doctors did, since the letter reports fatalities in children with rheumatic fever. This is not a condition for which the drug should be prescribed." He added that there had been no such reports in the United States.

Another spokesman for the FDA acknowledged that the agency was partly at fault in the wording it had authorized for the company's literature. "The use of the word 'antirheumatic' to describe indomethacin should never have been approved in the first place," he said.

He went on to suggest that since the agency felt that it was at least in part responsible for the problems that were being encountered, it had decide to work out the solutions together with the manufacturer. When the drug safety letter and the revised package insert had been sent out, the FDA spokesman said, "We felt that we had acquitted ourselves. We brought about immediate relief by having the company revise its package insert and stop the use of the violative advertising."

Asked why the FDA had made no announcements of the reported adverse reactions or the safety advisory letter, as it has done previously with other drugs, the spokesman said that the agency had ought to act in the public interest without taking public action. "We had no reason to make a public announcement." He stressed that the agency is eager to avoid charges of "regulation by press release."

In West Point, Pa., a Merck spokesman also commented on the differences between the FDA-approved U.S. letter to physicians and the sharply detailed Canadian letter. He suggested that the American letter served primarily as a covering note for the revised package insert that was enclosed. The Canadian letter, he said, represented the total extent of the information sent at the time to Canadian physicians and contained much of the data printed in the enclosed circular to the American profession.

DEPARTMENT OF NATIONAL HEALTH AND WELFARE,
FOOD AND DRUG DIRECTORATE,
Tunney's Pasture, Ottawa, March 29, 1968.

DR. WILLIAM D. HOWE, M.P.,
House of Commons,
Parliament Buildings,
Ottawa, Ontario.

DEAR DR. HOWE: In accordance with our telephone conversation of March 29th, I have enclosed for your use two copies of the "Dear Doctor" letter on Indocid which was distributed by the Directorate in November, 1966. I should like to point out that the several deaths reported in children to which reference is made in paragraph 4, did not take place in Canada.

The Directorate obtains information in regard to adverse reactions to drugs from the following sources:

1. Drug Adverse Reaction Reporting Program: These reports include information submitted to us by individual physicians and hospitals;
2. Adverse reactions reported to the Directorate by the manufacturer; and
3. Reports of adverse reactions which appear in the medical literature.

Under these circumstances, a count of the number of adverse reports received would not be meaningful since we are fully aware that we have not attained anything like total reporting. The Drug Adverse Reaction Reporting Program may, however, indicate a trend which, on subsequent investigation, leads us to definite adverse reactions.

I hope that this information will be helpful.

Yours sincerely,

R. A. CHAPMAN, *Director-General.*

DEPARTMENT OF NATIONAL HEALTH AND WELFARE,
FOOD AND DRUG DIRECTORATE,
Tunney's Pasture, Ottawa, Ontario, November 17, 1966.

DEAR DOCTOR: As you know, Indocid® (indomethacin—Merck Sharp & Dohme), a new anti-inflammatory agent for use in rheumatoid arthritis, ankylosing spondylitis, gout and severe osteoarthritis has been available for approximately one year in Canada. Recently, the Food and Drug Directorate has received a number of reports of adverse reactions, the severity or nature of which were unknown at the time the drug was released.

It is now apparent that indomethacin can mask the signs and symptoms of an infectious process or activate a latent bacterial infection. These complications are similar to those observed with corticosteroids and other anti-inflammatory drugs.

The possibility of a concurrent infectious process in your patents receiving indomethacin should be constantly borne in mind. If symptoms and signs suggestive of infection appear, discontinuation of the drug should be considered and vigorous therapy initiated.

Several deaths have been reported in children with severe forms of rheumatoid arthritis, dermatomyositis and rheumatic fever who were receiving indomethacin. Some of these children succumbed to an intercurrent infection, the severity of which may have gone unrecognized during treatment. The exact relationship to indomethacin was difficult to determine in these reports. However, we recommend that indomethacin should not be used in children until the results of further studies become available.

Headache, dizziness and minor confusion are described in the existing package and direction circular. However, it is pointed out that in patients receiving indomethacin in the recommended dosage, reactions relating to the central nervous system are not uncommon and can be severe.

Infrequently, leukopenia, thrombocytopenia, and granulocytopenia or agranulocytosis have been reported in conjunction with indomethacin. In addition to hemorrhage from the gastrointestinal tract which has been previously described, hematuria has been observed.

Blurred vision and changes in visual acuity have also been reported but a clear relationship to indomethacin has not been established. However, we suggest that any ocular complaints in patients on long-term therapy should be carefully investigated.

Merck Sharp & Dohme are presently revising their package insert and brochure to include information on these reactions. We are reporting these adverse reactions to you at this time, with the request that you notify the Drug Adverse Reaction Reporting Program of the Food and Drug Directorate if any such cases or other suspected reactions to indomethacin occur in your practice.

Yours very truly,

R. A. CHAPMAN, *Director-General.*

[From Clin-Alert, Apr. 11, 1967]

INDOMETHACIN

[No. 75]

A. *Asthma:* "Indomethacin (Indocin; Indocid-Merck Sharp & Dohme) has been widely employed in treatment of such conditions as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and gout. Major adverse reactions associated with indomethacin therapy involve the central nervous system and the gastrointestinal tract. The present report concerns a case in which the ingestion of indomethacin was associated with an acute asthmatic attack in a patient with intrinsic bronchial asthma, nasal polyps, and aspirin sensitivity. The relationship between indomethacin administration and asthma was documented by challenge with the drug."—Vanselow & Smith (Ann Arbor, Mich.), Ann. Int. Med. 66:568 (Mar.), 1967.

[Recent studies have shown that indomethacin is no more effective than aspirin in the treatment of rheumatoid arthritis (Donnelly et al., British M. J. 1:69, 1967; Pinals & Frank, New England J. M. 276:512, 1967). A Committee of the American Rheumatism Association made a survey of the literature on indomethacin extending back to its introduction in 1963. There were 46 reports which specifically dealt with the use of the drug in rheumatoid arthritis. The committee stated: "In general the degree of enthusiasm for the drug varied inversely with the quality of the investigation." A high incidence of side effects in proportion to therapeutic effect with indomethacin in rheumatoid arthritis was reported as early as 1963. Rubens-Duval & Villiaumey (1964) reported 72 per cent side effects in patients on a dose of over 200 mg. indomethacin daily, and Robinson (1965) could maintain therapy in less than 50 per cent of patients receiving 125 to 150 mg. indomethacin daily. (The maximum effective daily dose recommended by the manufacturer is 150 to 200 mg. daily.) Such observations suggest that the therapeutic index of the drug is low.]

B. *Unexpected Death:* "In mid-1966, Solomon, of Johannesburgh, South Africa, observed threee adult patients in whom indomethacin therapy apparently reactivated infectious conditions. Fortunately, the patients survived. Caution was urged in selection of patients to be treated with this drug (Clin-Alert No. 153, 1966). The present authors observed two indomethacin-treated children with rheumatoid arthritis who abruptly developed fatal febrile illness. Physical examination shortly before death revealed nothing to suggest impending disaster. In one patient, postmorten examination showed no definite cause of death. Group A beta hemolytic streptococcal septicemia appeared to be the immediate cause of death in the other. The manufacturer has knowledge of two additional cases of unexpected death in children receiving indomethacin and has issued a warning against the use of the drug in young patients (Clin-Alert No. 3, 1967)."—Jacobs (New York, N.Y.), JAMA 199:932 (Mar. 20, 1967).

[From Medical Tribune, Apr. 19, 1967]

MERCK MAY FACE PROSECUTION ON INDOMETHACIN ADVERTISING

WASHINGTON, D.C.—The manufacturer of indomethacin may face criminal prosecution for alleged violations in the drug's advertising, the Food and Drug Administration has disclosed. FDA officials said that a preliminary hearing has been held to give Merck Sharpe & Dohme the opportunity to answer charges of "serious violations" in its advertising of the anti-arthritic compound. Such a hearing is customarily ordered when criminal prosecution looms as a "possibility," MEDICAL TRIBUNE was told.

At the office of the FDA legal counsel it was learned that the manufacturer had submitted "additional documents" to buttress its reply to the charges and that these, as well as presentation of the manufacturer's "side of the case," were now under review.

The charges against indomethacin advertising were made public last October when William W. Goodrich, FDA's chief counsel, asserted that Merck and other manufacturers were making exaggerated claims or giving misleading impressions in their promotion.

Merck is facing the possibility of court action, however, because its alleged violations in indomethacin ads, an FDA official said, were of "longer standing, more intense, and more serious" than those of other drugs named by Mr. Goodrich.

In his charges, the FDA counsel had said that indomethacin was prematurely claiming that it "extended the margin of safety in the long-term management of arthritic disorders," that it omitted "some very important warning information" about adverse effects, and that it claimed "excellent results" in some cases of rheumatoid arthritis but omitted reference to "some striking failures as well."

Following the Goodrich statement, the FDA held further discussions with Merck and the company dropped all its indomethacin advertising late last year, an FDA official told MEDICAL TRIBUNE.

"Ordinarily, the withdrawal of advertising and the introduction at a later point of acceptable advertising would be sufficient," the spokesman said. "In the case of indomethacin, however, it was our feeling that the degree and extent of violations involved called for further action."

[From British Medical Journal, Apr. 29, 1967]

REGIMEN OF INDOMETHACIN THERAPY IN ACUTE GOUTY ARTHRITIS

(By B. T. Emmerson,* M.D., M.R.A.C.P.)

Though colchicine has been famed for centuries for its effect in acute gouty arthritis its relief of pain and inflammation in this condition is not invariable and may not be apparent for 24 hours or more. It was therefore not surprising that when phenylbutazone was introduced colchicine was largely replaced by this preparation, which was more certain in its action. High-dosage phenylbutazone therapy, however, was occasionally associated with marrow depression (Mauer, 1955). In 1963 indomethacin was reported to be an effective anti-inflammatory agent in a number of rheumatic diseases (Katz *et al.*, 1963; Norcross, 1963; Rothermich, 1963). In acute gouty arthritis Hart and Boardman (1963) reported favourable results with the use of 300 mg. of indomethacin given in divided doses during the first 24 hours, with a gradual subsequent reduction to 100–150 mg. daily. The dose was varied from day to day according to the response, and treatment was continued for at least five days, or longer if symptoms persisted. Smyth *et al.* (1963) also obtained good results with indomethacin in acute gouty arthritis, using doses of 600–900 mg. on the first day and 400 mg. daily in divided doses during the next three to five days.

It therefore seemed that indomethacin was useful in acute gouty arthritis, but that dosage schedules varied widely and needed frequent review. Thus there seemed a need for a standardized regimen of treatment which would be uniformly successful but simple enough to leave in the hands either of patients or of nursing staff without constant supervision, and which would vary inherently with the severity of the gout and the response. Such a schedule might well be comparable to the usual schedule of oral colchicine treatment, in which the dosage varied with the response and toxic effects. The above considerations therefore led to the choice of the following therapeutic regimen: 100 mg. of indomethacin four-hourly until most pain was relieved, then 100 mg. eight-hourly for 24 hours, then 75 mg. eight-hourly for 24 hours, and then 50 mg. eight-hourly for 24 hours.

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*Reader in Medicine, Medical Professional Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia.

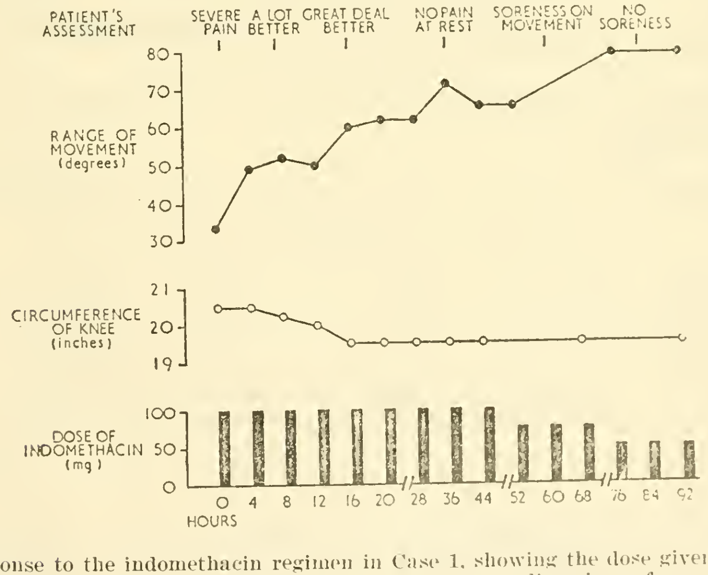
This regimen was tested for effectiveness in patients with acute gouty arthritis. At the same time undesirable side-effects were sought and opportunities were taken to determine whether improvement in the regimen, such as a reduction in dosage, was possible.

PATIENTS

Twenty-two patients (see accompanying Table) were treated with the above regimen over a period of two years. Initially, patients were observed in hospital, here regular assessment of response was made. Later a few were treated as out-patients and came to the hospital daily for assessment. The severity of the arthritis in this group varied greatly, but a large proportion had severe gout and had been referred because of difficulty in control of hyperuricaemia. In half of the patients more than one joint was acutely inflamed.

RESULTS

There was a rapid and striking response to this regimen of treatment with indomethacin, details of which are shown in the Table. The severe pain had usually begun to ease within a couple of hours, and relief of pain at rest was in most cases complete within 24 hours. Some patients with podagra were able to wear a shoe next day. A typical response (Case 1) is shown in the Chart, where t is seen that as the regimen produced subsidence of inflammation a steady increase in the range of movement in the knee and a reduction in the circumference of the joint occurred. In the Table the column entitled "Perference to Othr Therapy" refers to the patient's preference for indomethacin over other forms of treatment, such as colchicine or phenylbutazone, which had been administered for previous acute attacks. Those who developed second attacks of acute gouty arthritis were asked if they would agree to undergo treatment with either colchicine or phenylbutazone on the second occasion in order that the response could be compared with that to indomethacin. All declined, however, perferring to have indomethacin again, chiefly because of the rapidity of relief from pain.



Response to the indomethacin regimen in Case 1, showing the dose given at the various time intervals (in hours), with the corresponding circumference of the affected joint, the increasing range of movement, and the patient's subjective assessment of the pain at the different times.

RESPONSE OF PATIENTS WITH ACUTE GOUT TO INDOMETHACIN REGIMEN

Case No.	Sex	Age	Number of joints involved	Initial relief with first 100 mg.	Time for relief of spontaneous pain (hours)	Total dose	Preference to other therapy	Serum Creatinine	Blood urea		Associated diseases
								Mg./100 ml.			
1	Female	51	3	Yes	30	1,275	Yes	9·6	1·8	66	Obesity.
2	do	67	2	Yes	12	1,075	Yes	7·7	1·1	36	
3	Male	43	1	Yes	24	875	Yes	9·0	1·9	24	Hypertension and hyperlipaemia.
4	do	45	2	Yes	24	1,075	Yes	8·7	1·4	27	Hypertension.
			2	Yes	18	1,125	Yes				
5	do	48	1	Yes	16	1,075	Yes	8·2	1·0	33	Hypertension, obesity.
6	do	43	1	Yes	12	1,175	Yes	10·1	2·4	100	Gout nephropathy, hypertension.
7	do	45	1	Yes	24	825	No	7·6	1·1	32	Hypertension.
8	do	76	1	Yes	30	975	Yes	5·0	1·4	38	Duodenal ulcer, on probenecid.
9	do	60	1	Yes	18	875	No other therapy	7·9	1·3	50	Postoperative, first attack.
10	do	39	2	Yes	20	1,175	Yes	9·4	·9	24	Pancreatitis.
11	do	45	4 (gout for 6 weeks)	No	(1)	1,250	(2)	9·6	1·2	25	Alcoholism.
			1	Yes	30	1,050					
12	do	44	1	Yes	4	875	Yes	9·1	1·1	29	Hypertension, hypothyroidism, hypertriglyceridaemia.
			2	No	72	875	Doubtful				
13	do	47	1	Yes	30	1,075	Yes	8·9	1·5	50	Obesity, nephrolithiasis.
			3	Yes	48	1,175	Yes				
			1	Yes	60	350	Incomplete response				
14	do	29	2	Yes	32	1,575	Yes	13·0	1·4	31	Alcoholism.
15	do	50	1	Yes	24	975	Yes	7·2	1·6	47	Urinary tract infection.
16	do	45	1	Yes	20	875	Yes	4·5	1·7	42	Hydronephrosis, pyelonephritis; on allopurinol.
17	do	48	3	No	24	1,375	Yes	11·0	2·3	72	Gout nephropathy, renal calculi.
			2	No	24	875					
			1 (24 hours later)	Yes	12	875					
18	do	44	1	Yes	18	1,075	No other therapy	8·2	1·2	22	
19	do	55	4	No	24	975	Yes	16·0	1·0	64	Polycythaemia vera, myeloproliferative syndrome.
			1	No	48	1,600		17·0	1·0	48	
			1	Yes	28	875		15·0	1·0	53	
			2	Yes	24	1,050		8·1	1·0	43	On allopurinol.
			1	Yes	24	875		6·3	·9	28	
			1	Yes	8	300		5·7	·8	37	
			1 (20 hours later)	Yes	12	975		5·7	·8	37	
20	do	36	1	Yes	16	500	Yes	9·3	1·0	24	Hypertension.
			1 (16 hours later)		30	1,325					
21	do	44	1	Yes	12	300	Yes	11·1	1·0	22	Uric acid calculi.
			1 (24 hours later)	Yes		400					
22	do	50	2	Yes	16	975	No other therapy	9·2	1·2	34	First attack.

[1] Incomplete.

[2] Subsequent colchicine and phenylbutazone unsuccessful.

Opportunities also presented themselves for determining whether the dose of indomethacin could be reduced and yet an effective response be maintained. One patient (Case 13) taking 350 mg. of indomethacin in 30 hours for a mild attack of gout did not lose his pain at rest for 60 hours, and even then his arthritis responded only incompletely. Three patients (Cases 19, 20 and 21) either were given a small initial course of 300 to 500 mg. or the course had to be interrupted because of an intercurrent development. After the initial improvement in these patients relapse occurred within 24 hours, making necessary a further course of treatment, which was sometimes more than would have been expected had the interruption not occurred. On the other hand, the patient who did not respond to the indomethacin regimen (Case 11) did not respond to a subsequent course of colchicine or phenylbutazone. In retrospect it is thought that a response may have been obtained had the dostage of indomethacin been increased further. Five patients still had slight residual pains or signs of inflammation when the course of indomethacin was completed; because of this doses of 75 mg. of indomethacin a day were continued for a further one and four weeks. For these reasons it is not thought possible to lower the routine dose or to shorten the duration of indomethacin therapy to less than four days without the risk of recurrence of the gout. Even then one should be prepared to lengthen the regimen if complete subsidence has not occurred at that time, or to restart it if there is any early recurrence.

SIDE-EFFECTS

Patients were asked whether the indomethacin tablets had upset them in any way, and were later specifically questioned about symptoms of headache, giddiness, faintness, nausea, vomiting, dyspepsia, and diarrhea. Out of the 22 patients only four developed headache during the treatment; one of these thought that the relief of the gout was fair compensation for the headache, and two commented that they "often get headaches, anyway." One patient admitted to slight giddiness during treatment; two complained of "indigestion" and one of nausea when the indomethacin was taken on an empty stomach, with relief when taken after food. No patient was known to have a peptic ulcer. One patient noticed impairment for his capacity for mental concentration. Another (Case 20) developed vomiting and giddiness after 500 mg. of indomethacin, which was thereupon stopped. When his gout recurred 16 hours later he took a course of 1,325 mg. without further symptoms.

Because of the reported association with peptic ulceration (Norcross, 1963; Lövgren and Allander, 1964), the indomethacin capsules were given whenever possible with food, but antacids were used only if epigastric discomfort occurred. Tests for faecal occult blood (chiefly using Haematest tablets) were carried out on any faeces passed. As no dietary restriction before starting treatment was possible, interpretation of the results was difficult. Comparison of the results with those reported by Goldman *et al.* (1964) in patients on a normal diet, however, failed to show any difference in the incidence of positive reactions at the different reading times. Thus no evidence was obtained that the preparation and dosage used in this trial induced any significant degree of occult ailmentary-tract bleeding. No anaemia developed.

DISCUSSION

Apart from the mention of gout among reports of the use of indomethacin in other joint diseases (Barceló and Sans-Solá, 1965; Robinson, 1965; Nelson, 1966), the only other specific study of the use of indomethacin in gout is that of Boardman and Hart (1965), who treated 26 patients. They also commented on the rapidity of relief, as 61% of their patients treated with indomethacin obtained relief within 48 hours as opposed to 12% of those treated with phenylbutazone. Their dosage range, however, varied widely, from 50 to 400 mg. daily initially when using tablets and from 75 to 150 mg. daily latterly when using the capsules. Their final recommendation was for dosages ranging from 25 to 50 mg. six-hourly, the exact level being determined by personal experience in the individual case. This is much lower than the schedule under study, and, as described in the results, total daily doses similar to theirs were ineffective in a number of our patients. It is quite apparent, however, that the present dose schedule produced even greater and more rapid relief of pain than the lower dose range, as 18 out of 22 patients obtained relief within the first four hours, a matter of importance in such a painful condition. The decisive factor would seem to be the severity of the gouty arthritis.

Boardman and Hart (1965) reported no response to indomethaein in four females with gout, but the two females in the group under study responded in a manner quite indistinguishable from that of the males—again the difference in response may be one of dosage. It would seem that the higher the dosage used the more rapid the response and the greater the proportion of patients responding. The factors limiting dosage then become the cost and the incidence of side-effects.

Reports of the use of indomethacin in other joint diseases (Hart and Boardman, 1965; Smyth, 1965) have included a high incidence of headache, giddiness, nausea, or vomiting. The incidence seemed to depend largely upon the daily dose of indomethacin administered, ranging from 30 to 80% with daily doses of 100 to 200 mg. This trial has therefore been unusual for the low incidence of side-effects found. Boardman and Hart (1965), using doses which sometimes reached 600 mg. daily, found a 30% incidence of side-effects in their gouty patients; they also commented that these were not severe. Their lower dosage was therefore not associated with any reduction in the incidence of side-effects, though they thought that side effects were less severe in younger patients. It seems possible that patients with acute gout, who are relatively young and otherwise healthy, may be more tolerant of the side-effects of indomethacin than patients suffering from a chronic debilitating disease such as rheumatoid arthritis.

SUMMARY

The results of treatment with a regimen of indomethacin therapy in 22 patients with acute gouty arthritis are described. The regimen consisted in administering 100 mg. of indomethacin by mouth four-hourly until most of the pain was relieved, after which administration was continued at eight-hourly intervals with three doses of 100 mg., three of 75 mg., and three of 50 mg. This method has been shown to be very effective in producing rapid relief of pain and subsidence of the acute gouty arthritis and to be associated with a low incidence of side-effects.

I wish to acknowledge the assistance of the nursing staff of the university wards at the Princess Alexandra Hospital and their care in attending to details of administration and recording the response to treatment. I am grateful to Merck, Sharp, and Dohme (Australia) Pty. Ltd. for generous supplies of indomethacin (Indocid).

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[Clinical Notes]

[From Journal of the American Medical Association, May 8, 1967, vol. 200, No. 6]

Toxicity of Indomethacin—Report of a Case of Acute Pancreatitis*

(By Manuel Guerra, M.D.)

Since its recent introduction, the nonsteroidal chemical called indomethacin (1-[*p*-chorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid) has been used exten-

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sively as a new "antirheumatic"[1] drug that has anti-inflammatory,[2] analgesic, and antipyretic[3] activity. The side effects have been described by various authors. These were usually limited to the central nervous system, with symptoms of headache, vertigo, light-headedness, and disturbed sensorium; and to the gastrointestinal system, with the symptoms of cramping, epigastric pain, and peptic ulceration.[4]

We found no mention of pancreatic involvement recorded in the literature. In the case being reported, the patient's condition was not associated with biliary tract disease, alcoholism, or any of the other conditions usually considered important in the cause of pancreatitis. We believe this case gives evidence that indomethacin does have a direct and toxic effect on the pancreas.

REPORT OF A CASE

A 69-year-old Negro man was admitted to the hospital on Aug. 21, 1966, at 1:45 AM complaining of severe epigastric pain of sudden onset. He had had nausea and vomited twice before admission. He had never been an alcoholic or had abdominal pain before. There was no history of chronic indigestion or gallbladder disease. Several months prior to the patient's admission, mild pulmonary emphysema was diagnosed, and the patient was advised to stop smoking, which he did. On May 13, he complained of painful fingers and joints, and a diagnosis of degenerative osteoarthritis was made. Indomethacin was prescribed (25 mg, three times a day). He was on a regimen of this medication until he was admitted on Aug. 21.

Physical Examination.—An acutely ill man in the state of collapse, complained of very intense epigastric pain. He had a rapid thready pulse, was cold and clammy, had an oral temperature of 101 F (38.3 C), and had a 40 mm Hg drop in his usual blood pressure. He was nauseated and vomited sporadically. Examination of the chest showed very rapid heart beat and respiration. There was no evidence of rales on either side of the chest, but diminished respiratory sounds were noted. The abdomen was distended slightly and was very tender to palpation, especially on the epigastrium. There was rebound tenderness and muscle guard, with markedly diminished peristalsis. The results of rectal digital examination were not remarkable.

Laboratory Findings.—On the patient's hospital admission, examination of the blood revealed a hemoglobin value of 13 gm/100 cc and a white blood cell count (WBC) of 5,500/cu mm, with normal differential and normal results of urinalysis. The serum amylase value was 648 Somogyi units (normal, 60 to 160 units). Twelve hours later, the amylase value rose to 712 units, with serum glutamic oxaloacetic transaminase (SGOT), 95 units, and lactic dehydogenase (LDH). 500 units. (The normal values range for SGOT is 20 to 40 units and for LDH, 200 to 500 units). After the first 24 hours the amylase value dropped to 464 units. Blood counts were repeated at 24-hr intervals for three days, with no appreciable change. The blood urea nitrogen (BUN) level was reported normal, but the calcium level dropped below normal. At 72 hours, the amylase value was 333 units. Diagnostic thoracentesis of the left side of the chest for pleural fluid was not performed because of the extremely critical condition of the patient. An electrocardiogram, also done on admission, was normal except for sinus tachycardia.

Roentgenographic Findings.—On the patient's hospital admission, a flat plate of the abdomen showed the "colon cut-off" sign.[5,6,7] On the roentgenogram taken of the patient in an upright position, the diaphragm was slightly elevated but there was no evidence of free air under it. There was some blunting of the right costophrenic angle.

Hospital Course.—The clinical impression of this patient's condition was one of acute pancreatitis. A nonoperative course of treatment was decided upon. The patient was placed on a regimen of nothing administered orally, continuous gastric suction, intravenous fluids, and whole blood. Plasma would have been preferred but was not immediately available. Broad spectrum antibiotic therapy was instituted. Anticholinergic drugs, B-complex vitamins, and ascorbic acid were administered. Calcium therapy was given intravenously. The patient remained in critical condition for a week, and gradually his condition improved. He was discharged on the 24th hospital day asymptomatic.

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COMMENT

The clinical diagnosis of acute pancreatitis, in this case, was corroborated by an elevated serum amylase level and the positive "colon cut-off"[5-7] sign seen on the flat plate of the abdomen taken on admission. Chest roentgenograms a few days after admission revealed atelectasis and fluid on the base of the left hemithorax. The occurrence of this condition in pancreatic disease has been described previously.[6] [8] [9]

Acute pancreatitis can be produced by multiple mechanisms. The three most important etiologic categories are (1) biliary tract disease, (2) alcoholism, and (3) various other causes. In this case we ruled out biliary disease because of a normal gallbladder series. The upper-gastrointestinal tract series, done at 2 and 11 weeks after onset of illness, was reported normal. A thorough investigation regarding alcoholism and history of trauma was carried out. The results were completely normal. The patient denied having had any kind of digestive symptoms in the past.

The possibility of hereditary pancreatitis was also investigated, with negative results. There was no history of allergy. No signs or symptoms of infectious diseases were present. The level of calcium in the blood was reported to be within normal limits except for the low reading during the acute phase of the disease. Results of total lipid and cholesterol examinations were normal. Familial hyperlipemia was absent. There was no history or indication of diabetes mellitus.

Cases of drug-induced pancreatitis, such as that produced by prolonged use of corticotropin (ACTH) and corticosteroids,[10] chlorothiazide,[11] and isoniazid[12] have been reported. Among other drugs that have been described in the literature as the sulfonamids[13] and salicylates.[14] To our knowledge, there have been no reports of indomethacin being pancreatotoxic when given in therapeutic doses for extended periods of time. This possibility is strongly suggested here, as this patient was taking no other medication. It is hoped this article will stimulate laboratory research to find the answer.

Since dismissal from the hospital, this patient has gained weight, returned to work, and has remained asymptomatic.

SUMMARY

In a 69-year-old Negro man with acute pancreatitis due to indomethacin, all etiological factors known at the present time were considered, investigated, and ruled out. Indomethacin has not previously been described as being a pancreatotoxic agent. The practicing physician should be aware of the possibility of the development of acute pancreatitis in patients receiving indomethacin.

Generic and Trade Names of Drugs

Indomethacin—*Indocin.*
Isoniazid—*INH, Nieonyl, Nydrazid, Tyvid.*
Chlorothiazide—*Diuril.*
Corticotropin—*Acthar, Actrope, Solacthyl Injection, Duracton.*

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[From Clin-Alert, June 9, 1967]

INDOMETHACIN—ACUTE PANCREATITIS

[No. 128]

"Reference was recently made to the high incidence of side effects in proportion to therapeutic effect of indomethacin (Indocin; Indocid-Merck Sharp & Dohme) in rheumatoid arthritis (Clin-Alert No. 75, 1967). Prior to the current report there have been no published observations suggesting that the drugs is pancreatoxic. In this case a 69-year-old man became critically ill after receiving indomethacin in a dosage of 25 mg. three times a day for approximately three months. The clinical diagnosis of acute pancreatitis was supported by findings of an elevated serum amylase level and a positive "cut-off" sign observed on x-ray examination. The patient responded to medical therapy and was discharged free of symptoms on the 24th hospital day."—Guerra (Pittsburg, Texas), JAMA 200:552 (May 8), 1967.

[From Clin-Alert, July 1, 1967]

INDOMETHACIN—ANKYLOSING SPONDYLITIS DOSAGE

[No. 143]

"According to the manufacturer (Merck Sharp & Dohme), indomethacin ('Indocin'; 'Indocid') is indicated in treatment of rheumatoid (ankylosing) spondylitis and in this condition 'frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.' The maximum recommended dose, currently approved by FDA, is 200 mg. daily. On the basis of the present report, both statements might well be challenged. In 27 patients with ankylosing spondylitis, six-week courses of indomethacin and placebo proved to be essentially equal in therapeutic effectiveness. The maximum daily dose of indomethacin tolerated without severe side effects by 50 percent of patients was 150 mg. per day. The authors conclude that '. . . the role of this agent in the routine management of ankylosing spondylitis should be questioned.' "—Kinsella et al. (Montreal, Que., Canada). Canad. M.A.J. 96:1454 (June 3), 1967

[Medical Memoranda]

[From British Medical Journal, July 15, 1967]

HEPATITIS WITH BILIVERDINAEMIA IN ASSOCIATION WITH INDOMETHACIN THERAPY

Biliverdin is the first bile pigment formed in the catabolism of the haem portion of haemoglobin. In man biliverdin is almost entirely reduced to bilirubin, which is excreted in the bile. The development of biliverdinaemia and biliverdinuria in association with disease, or as an iatrogenic effect, has not been reported. We here present a case of biliverdinaemia and biliverdinuria which developed after the administration of indomethacin (1-*p*-chlorobenzoyl-5-methoxy-2-methylindol-3-acetic acid).

CASE REPORT

A man aged 46 was employed as an unskilled labourer not at risk of exposure to toxic materials or gases. He was admitted to hospital on 14 May 1966 with a four-year history of intermittent joint pains which had been treated with salicylates and phenylbutazone outside hospital. For three weeks before admission he was having indomethacin 75 mg. daily.

On 7 May he had noticed that his urine was green, and soon was off his food and complaining of occasional abdominal pains. The only relevant feature in his past history was that he had suffered from brucellosis in 1957.

On physical examination the skin of the whole body presented a greenish hue, most evident on the trunk, while the conjunctivae were of normal colour. The temperature was 100° F. (37.8° C.); pulse 76/min. and regular; respiratory rate 20/min.; weight 62.6 kg.; and height 160 cm. The liver was palpable 7.5 cm. below the right costal margin. It was firm but not tender. The spleen was not palpable, and there were no intra-abdominal masses. Both hands showed early changes of rheumatoid arthritis. No physical abnormalities were detected elsewhere.

Laboratory findings

Hb 13.9 g./100 ml; P.C.V. 47%; R.B.C. 4,800,000/cu. mm.; reticulocytes 1.8%; leucocytes 7,200/cu. mm., with a normal differential count; blood film—slight anisocytosis, some spherocytic forms, and very occasional poikilocytes, no basophilic, polychromatic, or nucleated erythrocytes; osmotic fragility of erythrocytes—initial lysis at 0.4% NaCl (control at 0.46% NaCl), complete lysis at 0.28% NaCl (control at 0.30% NaCl); E.S.R. 15 mm. in first hour (Westergren); one-stage prothrombin time 17 sec. (control 15 sec.); bone-marrow smear—normoblastic erythropoiesis, normal myeloid series.

The serum was of a definite green colour. The van den Bergh reaction was delayed direct and the total serum bilirubin 3.3 mg./100 ml. Serum aspartate aminotransferase, 55 i.u./l.; alanine aminotransferase 94 i.u./l.; alkaline phosphatase 55 K.–A. units/100 ml. Blood urea 30 mg./100 ml. and total plasma cholesterol 630 mg./100 ml. Total serum protein concentration 6.0 g./100 ml., with albumin 3.0 g./100 ml. Filter paper electrophoresis showed a slight reduction in serum albumin, with some increase in alpha$_1$- and alpha$_2$-globulins, a significant reduction in betagloulin, and some increase in gammaglobulins. Serum uric acid 6.2 mg./ml. and serum pseudocholinesterase 160 units/100 ml. (range of normal sera 130–310 units/100 ml.). The latex fixation tests for C-reactive protein and the R.A. factor were positive.

The urine was a dark green. It had a *p*H of 5.8 and contained a trace of protein but no blucose or reducing substances. No urobilinogen or urobilin was detected. Fouchet's test gave a strong green spot indicative of biliverdin. The diazo reaction was negative even on the addition of ethyl alcohol. The sediment contained only an occasional crystal of calcium oxalate. *Pseudomonas pyocyanea* was not cultivated from the urine. The faeces were green in colour and also gave a strong green spot with Fouchet's reagent.

The pigment in the urine was isolated in large quantities and identified as biliverdin by the absorption spectrum of its solution in 5% methanolic hydrochloric acid and that of its zinc complex after oxidation with iodine. The spectra observed agreed with those reported by Gray *et al.* (1961a; 1961b) for biliverdin.

Histological sections (Fig. 1) of liver tissue obtained by percutaneous puncture on 23 May showed centrilobular degeneration, swelling and some fatty change of parenchymal cells, and regeneration of hepatic cells. Both the parenchyma and portal zones contained many neutrophils and mononuclear cells, including plasma cells. Bile stasis, mostly with Kupffer cells, adjacent to the foci of necrosis was evident. van Gieson staining showed increased collagen deposition

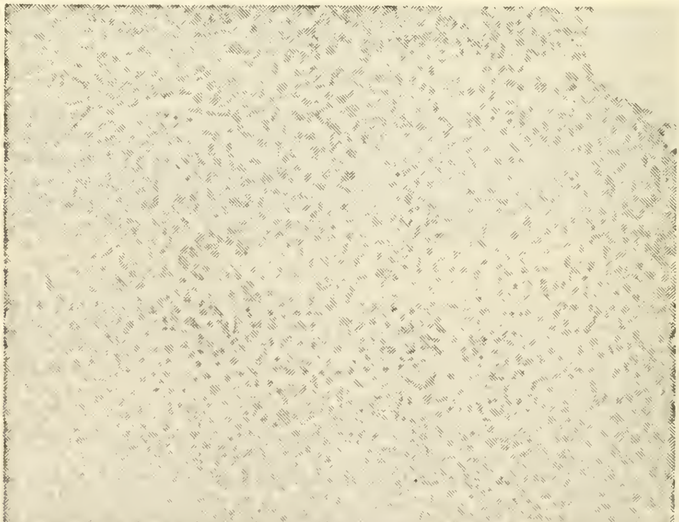

FIGURE 1.—Section of liver tissue. Centrilobular degeneration, swelling and some fatty change of parenchymal cells, and regeneration of hepatic cells. There is infiltration of both the parenchyma and portal zone by many neutrophils and mononuclear cells, including plasma cells. (Haematoxylin and eosin. ×165.)

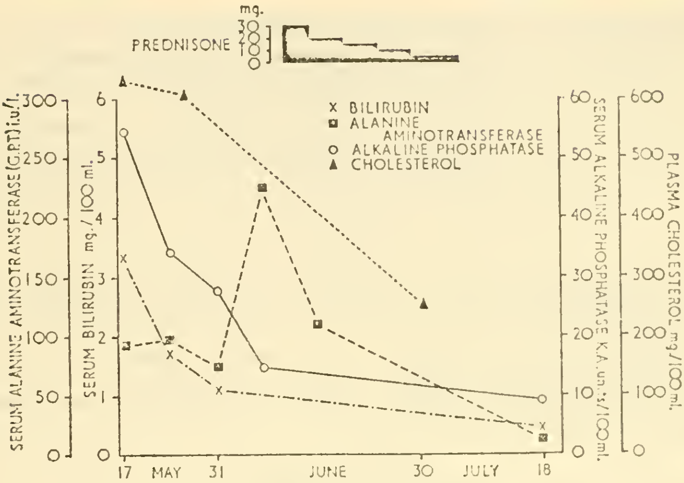

FIGURE 2.—Main biochemical changes during the period of observation.

around the central veins but no increase in the portal tracts. There was some bile-duct proliferation, but the ducts were not obstructed. The overall picture was that of an acute hepatitis.

Indomethacin therapy was stopped, and conservative treatment was instituted, with bed rest, a high protein and carbohydrate diet with elimination of fats, and parenteral vitamin supplements for the first three weeks.

The main biochemical changes during the period of observation are shown in Fig. 2. As the serum alanine aminotransferase rose considerably above the level on admission, prednisone was prescribed at an initial dose of 30 mg. daily. This was followed by sustained progress. Within six weeks of the start of prednisone therapy the liver was no longer palpable, the urine and faeces had regained their normal colour, and the serum chemistry became normal.

The patient was discharged from hospital on 5 August 1966 and has remained well.

COMMENT

Temporary mental or neurological symptoms, haemorrhages, haemocytopenias, and even fulminating infections has been reported in the course of indomethacin therapy (W.H.O., 1966). Bruckner and Randle (1965) reported hepatotoxicity associated with indomethacin, but the evidence they produced is very tenuous. In a personal communication the manufacturers claim that there has been no no proved case of hepatotoxicity produced by indomethacin. However, Kelsey and Scharyj (1967) have reported a case of fatal hepatitis which was probably due to indomethacin.

The tests of liver function employed and the histological changes in the liver seen in the case presented here are consistent with the diagnosis of cholestatic hepatitis similar to that produced by drugs such as chlorpromazine. In the present case salicylates and phenylbutazone had been taken several months before the illness, while indomethacin had been taken for three weeks before admission to hospital.

Biliverdinaemia presumably results from blockage of the reduction of biliverdin to bilirubin. Singleton and Laster (1965) have demonstrated the existence of high biliverdin reductase activity in guinea-pig liver and spleen. They also demonstrated biliverdin reductase activity in human liver. The development of biliverdinaemia and biliverdinuria has not yet been recorded. Two explanations for its occurrence may be suggested. It is possible that in producing hepatitis indomethacin severely inhibited the activity of biliverdin reductase in the patient's liver, and probably also in the spleen. It is also possible that the patient has a congenital partial deficiency of biliverdin reductase, which came to light as a result of the hepatitis.

We wish to express our thanks to Professor G. P. Xuereb, the Royal University of Malta Medical School, and to Dr. P. J. Scheuer, the Royal Free Hospital, London, for their helpful opinions on the histological sections, and to Dr. Barbara H. Billing, the Royal Free Hospital, London, for advice.

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[Letters to the Journal]

[From Journal of the Americal Medical Association, July 31, 1967, vol. 201, No. 5]

TOXICITY OF INDOMETHACIN

To the Editor:—The article "Toxicity of Indomethacin" (200:552, 1967) deserves comment and critical objections.

First, there is not the slightest proof in the reported case that the attack of acute pancreatitis was due to the indomethacin which the patient had been taking without ill effects for more than three months. Post hoc is not necessarily proper hoc. In the comment the author writes, "We ruled out biliary disease [as etiologic factor] because of a normal gallbladder series." This, however, is not mentioned in the report of the case, just as the gastrointestinal series taken two weeks after the onset is mentioned only in the comment.

The author, moreover, does not seem to realize that a normal biliary tract, by x-ray or by inspection (as published by me and others years ago), does not rule out a common channel between common bile duct and pancreatic duct, this common channel is thought by a good number of men to be the most frequent—but not the only—cause of acute pancreatitis. There is no doubt that in many cases of acute pancreatitis the pathogenic factor cannot be found. This, however, does not justify attributing it to medication the patient happened to be taking at that time. I wonder also what the author meant by a pancreatotoxic agent, and how that causes acute pancreatitis!

The phrase "in a 69-year-old Negro man with acute pancreatitis *due* to indomethacin" is not justified, and the title of the publication should have been "Acute Pancreatitis in the Course of Indomethacin Treatment." This can bring unjustified ill repute to a good medication.

HANS L. POPPER, M.D.
CHICAGO.

[Correspondence]

[From the Canadian Medical Association Journal, Aug. 12, 1967, vol. 97, pp. 345–347]

EVALUATION OF INDOMETHACIN IN ANKYLOSING SPONDYLITIS

To the Editor:

The paper on "Evaluation of Indomethacin by a Controlled, Cross-over Technique in 30 Patients with Ankylosing Spondylitis" by Drs. T. O. Kinsella, K. R. Mackenzie, S. O. Kim and L. G. Johnson (*Canad. Med. Ass. J.*, 96: 1454 [June 3], 1967) is in general an excellent study and I welcome its appearance. There are a few points worthy of discussion, and a study as good as this one can stand some criticism without major loss.

In the design of the study the indomethacin was added to previous medication, that is, was asked to solve therapeutic problems not solved by previous treatment. This presents a much tougher problem for the new drug than does a straight comparison of new treatment alone versus no treatment. Thus it is quite impressive that more than one-half of the patients found subjective relief of pain. If one looks at all the parameters assessed, one finds that the indomethacin group did better than the placebo group in every measure recorded. Indomethacin was at least twice as good for morning, stiffness and for chronic pain, more than twice as good for peripheral arthralgia, more than twice as often effective in improving cervical and lumbar mobility, and better in all other clinical assessments. Three times as many patients taking indomethacin had improvement of their sedimentation rate and alpha-2 globulin as compared with those taking a placebo. These figures did not reach statistical significance; but since all the independent measures were in the same direction, the trends would be highly significant if a sign test of significance were employed. One suspects that a larger series would have revealed very significant differences in the individual parameters, and it was unfortunate that the authors did not employ the techniques of sequential analysis. I realize the great difficulties in building a series of adequate size, but a false-negative result may be as unfortunate as a false-positive result. The data as presented suggest but do not prove that indomethacin was quite a bit better than placebo in this rather tough treatment challenge.

One minor point worth mentioning, because the error is so common, is the use of the word "random" in their phrase "48 patients were chosen at random". In the context of a clinical trial this would mean that some highly artificial method of selection was used in a deliberate effort to cancel out sources of bias, whereas in fact the patients were simply those available through the outpatient clinics and ward services of the participating physicians and were subject to all the unknown and uncontrollable selection factors of any teaching hospital group.

HUGH A. SMYTHE, M.D.,
Wellesley Hospital, Toronto.

To the Editor:

I have read with interest the paper entitled "Evaluation of Indomethacin by a Controlled, Crossover Technique in 30 Patients with Ankylosing Spondylitis", by Kinsella and colleagues (*Canad. Med. Ass. J.*, 96; 1454, 1967). At the present time indomethacin is being somewhat "over-promoted" in my opinion, and I think that this paper will help to give people a better sense of proportion. The authors are to be congratulated on the careful study.

From the experience we have had here it does seem that indomethacin has a significant effect in the occasional patient with spondylitis or rheumatoid arthritis. In these particular, though uncommon patients the drug seems to achieve effects that are not obtainable with other analgesic anti-inflammatory medications. We have one patient who is doing much better on indomethacin than on either aspirin or phenylbutazone as far as the symptoms of her spondylitis are concerned. I wonder whether. in the 30 patients studied by the authors, one or two patients were significantly improved by the administration of indomethacin. If there were only one or two, they would not alter the statistics of the total group evaluation, but the results would still be significant in relation to that person's previous or other therapy.

While it is obviously very important to evaluate data on a statistical basis, it seems important not to overlook the fact that in any group of patients with a particular condition, one patient may respond in a different manner; a switch-over from alternate or placebo medications in this individual may establish that the drug in question was undoubtedly responsible for the improvement.

An indisputable response in one patient may be lost in a statistical evaluation, but the fact might remain that one particular patient for some particular reason does in fact respond in a particular way different to the remainder of the group.

If the authors of this paper did not find a single patient who was significantly improved, as determined by repeated switches from drug to placebo. I think this is worth knowing. If perhaps one or two patients did have an indisputable improvement, I think this would be worth recording also and perhaps be of value in establishing the true place of indomethacin therapy in rheumatic disease.

DENYS K. FORD, M.D., M.R.C.P. (Lond.), F.R.C.P.[C],
Associate Professor (Medicine), University of British Columbia,
Vancouver, British Columbia.

To the Editor:

The critical evaluations by Dr. Smythe and by Dr. Ford of our paper "Evaluation of Indomethacin by a Controlled, Cross-over Technique in 30 Patients with Ankylosing Syondylitis" are greatly appreciated. We welcome the opportunity to clarify some of the points that they have raised.

Dr. Smythe is, of course, correct in stating that a truly "random" selection of patients in a clinic setting is virtually impossible. Indeed, it should be noted that the text specifically stated that only patients with "clearly defined and persistent symptomatology were started on therapy".

It is difficult to comment on Dr. Smythe's interpretation of our data. The statistical method employed was one which has been specifically designed for this type of study. If there is any validity at all in employing statistical analysis of a drug study, then, quite frankly, it seems specious to conjecture that another method of analysis or a larger series or some other artificial manipulation would have produced a more desirable result. Accordingly, in spite of the interpretation postulated by Dr. Smythe, we can find no justification to modify our interpretation of our data.

The point raised by Dr. Ford is important and pertinent for the reason that he stressed. On completion of the study three patients expressed a preference for indomethacin. One of these patients had had marked subjective and objective improvement with indomethacin but, finally, the drug had to be withdrawn after several variations in dosage because of severe central nervous system and gastrointestinal side effects; the second patient, who was considered to be an unreliable observer, experienced subjective but not objective improvement and continues on indomethacin; the third patient has been lost to follow-up. Thus, Dr. Ford is correct in calling attention to the fact that the occasional "spondylitic" does have a thoroughly beneficial response to indomethacin, a point which is substantiated by our personal experience with patients not included in this study.

Before concluding, there is one point which we feel should be repeatedly stressed in view of the inordinate over-promotion which has been given to indomethacin. In one of the concluding sentences of our article we noted that we could not discern any preferential role for indomethacin in the treatment of patients with ankylosing spondylitis. To date we have encountered no new data which would lead us to alter this conclusion in so far as the management of the vast majority of patients with spondylitis is concerned.

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[From Clin-Alert, Aug. 31, 1967]

INDOMETHACIN

[No. 180]

A. *Temporal Arteritis*: "Temporal arteritis with the inherent risks of visual loss is a frequent complication of polymyalgia rheumatica. A case is presented to illustrate this relationship and to suggest that non-steroid anti-inflammatory agents, such as indomethacin (Indocin; Indocid-MS&D) may not prevent the development of arteritis in such patients. An elderly woman with low back pain and radiographic evidence of osteoarthritis of the hip and spine was first treated with aspirin and subsequently with indomethacin without improvement. She was then given phenylbutazone and an analgesic compound for approximately three weeks with no appreciable results. The patient was then directed to take 25 mg. indomethacin daily for one week, 25 mg. twice daily for one week, and finally, 25 mg. three times daily. The patient felt much better on this treatment but after about one month noted some visual disturbance and complained of bilateral and localized temporal tenderness. The dosage of indomethacin was reduced to 25 mg. daily. The headaches persisted and the drug was withdrawn.

At this point the patient noted diminished vision. A diagnosis of temporal arteritis was made and prednisone started immediately. Within two days, however, visual loss was complete. The authors note that the syndrome of polymyalgia rheumatica often responds to corticosteroid therapy and that temporal arteritis is less likely to develop in patients so treated. However, many physicians are reluctant to use steroids in the management of elderly patients with relatively minor musculoskeletal symptoms. Consequently, a non-steroid drug is often employed. It is of interest and possible importance that in this case, temporal arteritis developed while the patient was receiving therapeutic doses of indomethacin."—Easterbrook et al. (Montreal, Que., Canada), Canad. *M.A.J.* 97:296 (Aug. 5), 1967.

B. *Biliverdinemia*: "Biliverdin is the first bile pigment formed in the catabolism of the heme portion of hemoglobin. In man biliverdin is almost entirely reduced to bilirubin, which is excreted in the bile. The development of biliverdinemia and biliverdinuria in association with disease, or as an iatrogenic effect, has not been previously reported. In the present case a 46-year-old man who had been taking indomethacin for three weeks for intermittent joint pain noted that his urine was green. On physical examination the skin of the patient's body showed a greenish hue, while the conjuctivae were of normal color. Liver function tests and histological sections of the liver obtained by percutaneous puncture were consistent with a diagnosis of cholestatic hepatitis similar to that produced by drugs such as chlorpromazine. The pigment in the urine was isolated in large quantities and identified as biliverdin. Indomethacin was withdrawn and the patient recovered. It is possible that in producing hepatitis, indomethacin severely inhibited the activity of biliverdin reductase in this patient's liver. It is also possible that in this case the patient had a congenital partial deficiency of biliverdin reductase, which became evident as a result of the drug-induced hepatitis."—Fenech et al. (Malta), British M.J. 3:155 (July 15), 1967.

[From Clin-Alert, Feb. 22, 1968]

Indomethacin—Critical Review of the Literature

[No. 45]

"A review was made of all publicly available, archival sources of information on the use of indomethacin ('Indocin'; 'Indocid'; 'Indomee'; 'Amuno'-MS&D) in management of rheumatic diseases. In rheumatoid arthritis, early favorable uncontrolled evaluations were not confirmed by subsequent controlled studies. Indomethacin may be useful in other rheumatic diseases (few comparative studies have been made) but the drug is no more effective than aspirin in treatment of rheumatoid arthritis. The frequency and severity of undesirable side effects of indomethacin are of prime concern. In 15 studies reporting the prevalence of such effects, no fewer than *35 per cent* of patients had at least one undesirable reaction. In 14 studies which reported the number of patients forced to discontinue therapy, *20 per cent could not tolerate* the drug. Gastrointestinal side effects occur in many indomethacin-treated patients (approximate incidence: nausea, 12 per cent; diarrhea, 10 per cent; severe abdominal pain, 3 per cent; peptic ulcer, 2 per cent). *Severe frontal headache* is observed in 25 per cent of patients. [According to British investigators (Clin-Alert No. 52, 1966) it is unwise to ignore and dangerous to suppress headache so commonly encountered in patients receiving indomethacin. If headache persists upon reduction in dosage, *treatment should be discontinued.*] Much of the information on indomethacin is in the form of privileged, unpublished data submitted to the Food and Drug Administration by the manufacturer. Such data is accepted by FDA in support of therapeutic claims but the information is not available to the clinical investigator. The author notes that the physician '. . . must rely on the judgements of the officials of the drug company and the Food and Drug Administration, and *neither group* appears to have the *perspective* or expert *clinical knowledge* to objectively analyze this information. It might better serve the public interest if only fully published, public data were allowed as evidence supporting therapeutic claims." [Emphasis ours]—O'Brien, W.M. (University of Virginia School Med., Charlottesville, Va.). *Clin. Pharmacol. & Therap.* 9:94 (Jan.–Feb.), 1968.

APPENDIX II

LETTER TO SENATOR NELSON FROM E. B. ANDERSON, VICE PRESIDENT, HOFFMANN-LA ROCHE INC., DATED JANUARY 2, 1968, RE DRUGS

HOFFMANN-LA ROCHE INC.,
Nutley, N.J., January 2, 1968.

Hon. GAYLORD NELSON,
Chairman, Senate Monopoly Subcommittee,
U.S. Senate, Washington, D.C.

DEAR SENATOR NELSON: I want to thank you for the opportunity which you have given us to meet with your staff concerning recent statements which have been issued on the prices paid by certain government authorities for two Roche products. It was most helpful to review together the data which had been accumulated.

Hoffmann-La Roche Inc. shares your belief in the desirability of uniform pricing policies under which government agencies purchasing equal quantities of the same drug product would receive the same price. For some time Roche has had in effect a pricing policy designed to meet this objective, under which any Federal, State or local government which purchases from Roche is charged the same price for the same quantity of the same product.

On December 19, 1967, you issued a public statement and a price table which referred to the prices of several drug products, two of which are sold by Hoffmann-La Roche Inc., chlordiazepoxide hydrochloride and sulfisoxazole. Since several figures contained in the statement and in the survey data released at the same time are incorrect, I am writing to you to provide the correct information, as I am sure you want the record to be as accurate as possible. We also believe that some explanation of other items in the statement and the price table would permit a more meaningful comparison of prices for these two products.

In addition to the statement in the hearing, there was an additional statement by your office released on December 24, 1967, relating to the prices paid by various government purchasers for LIBRIUM capsules (chlordiazepoxide hydrochloride). This later statement, as reported in the *New York Times* of December 25, 1967, and several other papers, also contains some incorrect figures and conclusions which we are sure you would like to see corrected.

In several instances the statements and the table have confused prices for 25 mg. capsules of chlordiazepoxide hydrochloride with prices for 10 mg. capsules of the same drug. As a result, the prices for different dosages have been compared, which is obviously misleading.

A. CHLORDIAZEPOXIDE HYDROCHLORIDE

We have included hereafter the items in the statement and the price table of December 19, and the statement of December 24, relating to chlordiazepoxide hydrochloride which are not in accord with the facts, or which we believe leave an erroneous impression which should be corrected.

1. In regard to the City of Des Moines, the table states that the city pays the highest price of $45.00. While it does not state that Roche sold the product to Des Moines at this price, some persons may have so inferred. Actually, there are no direct sales of chlordiazepoxide hydrochloride to the City of Des Moines by Hoffmann-La Roche Inc. Since Roche has had no direct dealings with Des Moines for this product, the city's purchase of this product would have been from a wholesaler or retailer. As in the case of Des Moines, the cities of Cleveland and Paterson do not buy directly from Roche. Thus, the prices paid by those cities for Librium are presumably paid to wholesale or retail distributors.

Roche has made some direct sales to county hospitals where these cities are located, but the prices in the table and statement are not the prices which we have charged for these sales. Broadlawns Polk County Hospital (Des Moines) and Highland View Hospital in Cuyahoga County (Cleveland) have purchased Librium *25 mg.* capsules in bottles of 500 for $39.60, which is our price to direct government purchasers which do not buy the 5,000-capsule bottle or in quantities large enough to support a contract. Preakness Hospital in Passaic County

(Paterson, New Jersey) has purchased Librium 25 mg. capsules in bottles of 50 capsules at a price of $4.40 per bottle which is our price for that size bottle. The District of Columbia, we understand, purchases its requirements of Librium from a Veterans Administration depot.

I am sure you understand that the manufacturers of many different types of products cannot sell directly to all end-users, and, as a result, the prices paid by end-users will vary. In addition to direct sales to large-volume users, it is essential that Roche sell through drug wholesalers and retailers in order to serve adequately all of the small-volume purchasers. We, of course, have no control over the prices charged by other persons who distribute our products after we sell to them.

2. The information you received from the City of Philadelphia stated that Philadelphia paid $18.50 for 500 *25 mg.* chlordiazepoxide hydrochloride capsules. Our contract with Philadelphia signed on June 12, 1967, in fact specifies a price of $28.50 per 500 *25 mg.* capsules for a quantity in excess of 100,000 capsules. The price quoted in the statement, namely $18.50, refers to bottles of 500 *10 mg.* capsules for a quantity in excess of 250,000 capsules. In addition, it was stated that New York City paid $28.50 per 500 *25 mg.* capsules of chlordiazepoxide hydrochloride. That was our previous price to New York City. The current contract, which was effective October 1, 1967, calls for $25.50 per 500 *25 mg.* capsules, based on a quantity in excess of 500,000 capsules.

3. The statement noted that the Defense Supply Agency paid $13.20 per 500 *25 mg.* capsules of chlordiazepoxide hydrochloride. Actually, the price of $13.20 per 500 capsules is for *10 mg.* capsules under a contract for over 20 million capsules. Our contract with the Defense Supply Agency for capsules of the *25 mg.* strength calls for a price of $24.00 per 500 capsules in a total purchase of over 3,000,000 capsules.

4. Your information that Philadelphia got a better price than the Veterans Administration for *25 mg.* capsules of chlordiazepoxide hydrochloride is incorrect. As noted above, Philadelphia paid Roche $28.50 per 500 *25 mg.* capsules, based on the purchase of over 100,000 capsules. The Veterans Administration paid $21.75 per 500 *25 mg.* capsules based on a contract purchase of over 5,000,000 capsules. As can be seen, the Veterans Administration pays a lower unit price for capsules of the equal strength because it buys in greater volume.

5. The article also states that "Los Angeles paid a premium price even though it bought three times the quantity Philadelphia bought." This statement is incorrect. As the following table shows, for *10 mg.* capsules Los Angeles paid Roche a lower price based on a quantity purchase of over 1,000,000 capsules than Philadelphia paid based on a quantity of over 250,000; and for *25 mg.* capsules Philadelphia paid Roche $28.50 based on a quantity of 100,000 and Los Angeles paid $25.50 based on a quantity of 500,000:

	10 mg.	*25 mg.*
Philadelphia	$18.50	$28.50
Los Angeles	16.50	25.50

6. The prices listed in the article for the cities not covered above are also consistent with Roche's policy of equal prices for government buyers which purchase equal quantities of the same drug from Roche. The cities of Wichita, Kansas; Newark, New Jersey; and Grand Rapids, Michigan, all have paid $39.60 per 500 capsules of the *25 mg.* strength of LIBRIUM. This is the Roche price for a bottle of 500 *25 mg.* capsules, to direct government purchasers who do not buy large sizes, such as the bottle of 5,000 capsules, or annual quantities large enough to justify a contract purchase.

B. SULFISOXAZOLE

The statement and price table of December 19 also contain information on sulfisoxazole which we believe may lead to some erroneous inferences and therefore require further explanation.

1. In regard to the City of Des Moines, the table states that the city paid $25.30 per bottle of 1,000 *0.5 gram* sulfisoxazole tablets. Roche does not sell this product directly to Des Moines. Purchases of Roche's sufisoxazole by the City of Des Moines would have been from a wholesaler or retailer, or Des Moines may have purchased sulfisoxazole from another company.

2. The table quotes a price of $6.90 for a bottle of 1,000 *0.5 gram* sulfisoxazole tablets to the City of Philadelphia. The current Roche contract for sulfisoxazole with Philadelphia, dated June 12, 1967, calls for a price of $9.00 per bottle of 1,000 tablets based on a quantity of 1,000,000 tablets.

3. The prices cited in the table of $8.35 and $8.50 per 1,000 *0.5 gram* sulfisoxazole tablets paid to Roche by the Defense Supply Agency and the Veterans Administration, respectively, are below that paid by Philadelphia because they are supplied under contracts for very much larger quantities.

As you can see in the above items, much of the information upon which you relied regarding the prices for Roche products is inaccurate. We believe that, left uncorrected, these inaccuracies reflect adversely on the reputation and policies of Roche, and upon your Subcommittee. Accordingly, we respectfully request that the records of your Subcommittee be corrected to reflect the facts regarding the Roche prices and policies as stated herein. We appreciate the cooperation which both you and your staff have given us in reviewing this data.

Very truly yours,

E. B. ANDERSON, *Vice President.*

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